UNIV. OF
TORONTO
LIBRARY

P
Mad
M

The University of Minnesota

CONTRIBUTIONS FROM THE DEPARTMENT OF ANATOMY

VOLUME 8

1922-1923

244695
17.6.30

MINNEAPOLIS
Published by the University of Minnesota
1924

CONTENTS

The following papers have been published during the years 1922-192
Papers marked with an asterisk (*) are not included in this volume.

Bessesen, Alfred N., Jr., and Carlson, Herbert A. 1. Postnatal growth i weight of the body and of the various organs in the guinea pig. *Th American Journal of Anatomy,* 31:483-521 (1923).

Bessesen, D. H. 1. Changes in organ weights of the guinea pig during e
9 perimental scurvy. *American Journal of Physiology,* 63:245-256 (1923

Brenton, Helen. *1. Climate and race as factors influencing the weight of the newborn. *American Journal of Physical Anthropology,* 5:237-249 (1922).

Calkins, L. A. 1. Morphometry of the human fetus with special reference
7 to the obstetric measurements of the head. *The American Journal o Obstetrics and Gynecology,* 4:3-24 (1922).

Dunn, Halbert L. *1. Growth of the gray and white matter of the cerebra hemispheres from the third fetal month to adult life. (Abstract. Proceedings of The American Association of Anatomists. Thirty-nint session. *Anatomical Record,* 25:127 (1923).
2. The statics of the human arch when subjected to body weight. *Th
4 Military Surgeon,* June: 1-64 (1923).

Dunn, Louis and Dunn, Halbert L. *1. The significance of palpable lymph nodes in the new-born infant. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-ninth session. *Anatomical Record,* 25:127 (1923).
2. A statistical analysis of the causes of palpable lymph glands in the
5 new-born. *American Journal of Diseases of Children,* 25:[illegible]
(1923).

Gantz, S. J. Z. 1. Studies on the fetal development of the human jaws and teeth. *Dental Cosmos,* February:3-12 (1922).

Herrick, Ruth and Rasmussen, A. T. *1. The volume of the normal mal adult hypophysis and its various parts. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-ninth session *Anatomical Record,* 25:133 (1923).

Jackson, C. M. 1. Graduate instruction in anatomy. *American Medica Association Bulletin,* 15:61-67 (1921).
2. Dystrophic morphology and its significance. *Science,* 57:537-54 (1923).

Jackson, C. M. and Carleton, Rachel. 1. Organ weights in albino rats with experimental rickets. *Proceedings of the Society for Experimenta Biology and Medicine,* 20:181 (1922).
2. The effect of experimental rickets upon the weights of the variou organs in albino rats. *The American Journal of Physiology,* 65:1-1 (1923).

Johnston, J. B. *1. Survey of forebrain morphology. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-ninth session. *Anatomical Record*, 25:136 (1923).

11 2. Further contributions to the study of the evolution of the forebrain. *The Journal of Comparative Neurology*, 35:337-481 (1923).

12 3. Further contributions to the study of the evolution of the forebrain. V. Survey of forebrain morphology. *The Journal of Comparative Neurology*, 36:143-192 (1923).

13 Maeder, Leroy M. A. 1. Changes in the mammary gland of the albino rat (Mus norvegicus albinus) during lactation and involution. *The American Journal of Anatomy*, 31:1-26 (1922).

14 Miller, Shirley P. 1. Effects of various types of inanition upon the mitochondria in the gastrointestinal epithelium and in the pancreas of the albino rat. *The Anatomical Record*, 23:205-210 (1922).

Noback, G. J. *1. On the growth of the larynx, trachea, bronchi and lungs during the fetal and neonatal periods, with a consideration of their vertebral levels through infancy and childhood. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-ninth session. *Anatomical Record*, 25:144 (1923).

15 2. The developmental topography of the larynx, trachea and lungs in the fetus, new-born, infant and child. *American Journal of Diseases of Children*, 26:515-533 (1923).

Osterud, Hjalmar L. 1. Postnatal changes in weight and structure of the reproductive tract in the female albino rat. *Papers from the Mayo Foundation and the Medical School.* W. B. Saunders Company, Philadelphia and London. 2:218-232 (1923).

Rasmussen, A. T. 1. The glandular status of brown multiocular adipose tissue. *Endocrinology*, 6:760-770 (1922).

2. Experimental demonstration of the entire course of four descending tracts by a single alcoholic injection in the mid-brain. *Proceedings of the Society for Experimental Biology and Medicine*, 20:104-107 (1922).

3. The so-called hibernating gland. *Journal of Morphology*, 38:147-205 (1923).

Rasmussen, A. T. and Herrick, Ruth. 1. A method for the volumetric study of the human hypophysis cerebri with illustrative results. *Proceedings of the Society for Experimental Biology and Medicine*, 19:416-423 (1922).

Rogers, Lee. 1. Observations on the developmental anatomy of the temporal bone. *Papers from the Mayo Foundation and the Medical School.* W. B. Saunders Company, Philadelphia and London. 2:455-469 (1923) and the *Annals of Otology, Rhinology, and Laryngology*, 30:103-129 (1921).

Scammon, Richard E. 1. A summary of the anatomy of the infant and child. *Pediatrics by Various Authors* (Abt. Ed.) 1:257-444 (1923).

22 2. The height-weight index of the newborn infant. *Proceedings of the Society for Experimental Biology and Medicine*, 20:102-104 (1922).

Scammon, Richard E. and Calkins, L. A. *1. New empirical formulae for determining the age of the human fetus. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-ninth session. *Anatomical Record,* 25:148 (1923).

2. Simple empirical formulae for expressing the lineal growth of the human fetus. *Proceedings of the Society for Experimental Biology and Medicine,* 20:353-356 (1923).

Scammon, Richard E. and Dunn, Halbert L. *1. The postnatal growth in weight of the human brain and its parts and of the spinal cord. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-ninth session. *Anatomical Record,* 25:149 (1923).

2. Empirical formulae for the postnatal growth of the human brain and its major divisions. *Proceedings of the Society for Experimental Biology and Medicine,* 20:114-117 (1922).

Welch, Elwyn H. 1. Development of the musculature of the stomach with special reference to its condition in the newborn child and the premature infant. *Papers from the Mayo Foundation and the Medical School.* W. B. Saunders Company, Philadelphia and London. 2:3-23 (1923).

AUTHORS' ABSTRACT OF THIS PAPER ISSUED
BY THE BIBLIOGRAPHIC SERVICE, APRIL 2

Reprinted from THE AMERICAN JOURNAL OF
ANATOMY, Vol. 31, No. 5, May, 1923

POSTNATAL GROWTH IN WEIGHT OF THE BODY AND OF THE VARIOUS ORGANS IN THE GUINEA-PIG

ALFRED N. BESSESEN, JR., AND HERBERT A. CARLSON

Institute of Anatomy, University of Minnesota, Minneapolis

TWENTY-FIVE CHARTS

Owing to the convenient size, hardy nature, and rapidity of growth, the guinea-pig (Cavia cobaya) has been extensively used in various fields of biological and medical research. In order to understand the effects of experimental procedure upon the form and size (weight) of the body and of the various organs, it is necessary to know the process of normal growth and the normal variability of the body and its parts. In the absence of this knowledge, and with only a few controls usually available for comparison, the results of experiments upon the guinea-pig are always in serious danger of misinterpretation. Further data are also of interest in contributing to our knowledge of the growth of mammals in general.

Since nothing has been done to establish norms of postnatal growth for the organs of the guinea-pig, the present investigation was undertaken. Its primary purpose is to determine the normal growth curves for the weight of the various systems and individual organs from birth up to adult animals weighing over 1000 grams. Incidentally the growth of the body as a whole was also studied (up to 700 grams), for comparison with the more extensive data published by Minot ('91).

This investigation extended over a period of more than two years. It was done in the Institute of Anatomy of the University of Minnesota under the direction of Prof. C. M. Jackson, whom we wish to thank for aid and encouragement. We are also much indebted to Prof. R. E. Scammon, especially for assistance in calculating the growth formulas. The series of animals used is not extensive, but is considered large enough to warrant general conclusions and to give an approximate idea of the average normal growth and variability.

MATERIAL AND METHODS

Of the eighty-two guinea-pigs used in this study seventy-four were reared in the laboratory, from sixteen females and two males obtained locally. These breeding animals were all large and healthy. The other eight were all adults over 700 grams obtained from other local sources, and are represented by the following body weights: 790, 835, 910, and 927 grams (males) and 807, 810, 852, and 997 grams (females). Four of the females in the upper portion of the series were found at autopsy to be in early stages of pregnancy. These weighed as follows: 807, 852, 907, and 997 grams. The pregnancies apparently did not alter to any notable extent the weight of any of the organs studied.

The guinea-pigs were well cared for in well-lighted and ventilated rooms, which were steam-heated. The breeding females were usually kept in a large breeding pen (about 4 feet square) with the males until they became pregnant. The pregnant females were removed to smaller pens before giving birth to the litter. After weaning their young, the mothers were again put back into the large breeding pen.

The pens were at all times supplied with fresh water, hay, and oats. Some green food, either grass or cabbage, was supplied constantly, and carrots were also fed at least once a week. The pens were kept clean and dry.

During the first week of life the small guinea-pigs were weighed each day, as far as possible; for the next two weeks every two or three days; and later they were weighed every week until killed for autopsy.

In order to ascertain the growth of the various organs, both males and females were chosen at various definite body weights from new-born to adult. Four new-borns were autopsied, and the others at intervals up to about 1100 grams of body weight. Those selected were scattered so as to give a somewhat continuous series as shown by the individual body weights indicated in chart 2 and following charts. In fifty-eight cases, the autopsy was complete, the various systems as well as the individual organs being weighed. In the remaining twenty-four cases the autopsy was incomplete. In these cases only the viscera were weighed, excluding skin, skeleton, musculature, spinal cord, stomach, and intestines.

Charts were plotted as field graphs with the weight of the particular organ or parts (also body length) as the ordinate and the gross body weight as the abscissa (charts 2 to 25). The amount of scattering of the individual data indicates roughly the variability in weight of the corresponding organ or part. Averages for about each 100 grams of body weight were then calculated and inserted on the graphs. These averages are indicated by encircled crosses. With these averages as guides an approximately average growth curve was drawn on each chart.

An attempt was then made to derive a mathematical formula to fit each growth curve. As simple formulas were desired, the more complicated curves have been divided into two or more phases with separate formulas for each phase. In these formulas: Y = weight of the organ or part in grams; X = weight of body in grams; a, b, c = constants. The final growth curves representing these formulas are shown in charts 2 to 25.

The data shown represent the observations of two workers, the guinea-pigs up to a body weight of 730 grams having been autopsied by one (Bessesen); those above 730 grams by the other (Carlson), who is also responsible for the calculation of the formulas.

Of the organs weighed all were plotted out satisfactorily except the thymus, which is poorly defined, especially as age advances, and is difficult to distinguish from the surrounding adipose tissue. There was a great individual variation in the observed weight of the thymus, even in guinea-pigs of the same age or size.—This was doubtless due in a large measure to errors in technique of removal. Microscopical examinations were not made to determine the amount of thymus tissue present in the mass removed. Because of the unsatisfactory results obtained, the thymus data will not be included in the present report. Payton and Goodall ('04) and Payton ('05, '11) give some data on the growth of the thymus, which may be referred to by those interested.

Whenever possible the individual data of Lazareff ('95), which are quoted in part by Mühlmann ('99), will be inserted (as squares) in the charts. Lazareff worked on the effects of inanition upon the organs of guinea-pigs, but also included ten normal controls in his data. Only males were used in his investigation and the following organs weighed: lungs, heart, liver, spleen, kidneys, pancreas, stomach, intestines, bladder, skin, spinal cord and brain. The body weights of his normal animals were as follows: 522, 540, 540, 546, 547, 575, 610, 612, 670, and 674 grams.

AUTOPSY TECHNIQUE

The guinea-pigs selected for autopsy were weighed and then killed by chloroform. As soon as the animal was dead, the length was taken with calipers, measuring from the anus to the tip of the nose, with the body stretched out. The animal was then decapitated with a knife, the incision extending in a plane just posterior to the occipital bone and the angle of the mandible. The vertebral column was separated from the head and the spinal cord cut at the foramen magnum. The cervical structures were divided just anterior to the larynx. The body was suspended in order to drain out the blood (which was not measured). The head was then weighed and its integument removed. (To avoid evaporation, the various structures on being removed were placed in moist chambers until weighed.) The eyeballs were thus exposed and were removed and trimmed free from the attached conjunctiva, muscles, optic nerve, etc. The cranial vault was opened, the dura cut, and the brain removed, the cranial nerves being cut close to the brain. The hypophysis was next carefully removed, and the remainder of the head was put into a moist chamber with the integument.

The trunk was then taken. The thyroid gland was first dissected out. The integument was cut down the midline and the sternum together with the costal cartilages removed, care being taken not to open the peritoneal cavity. The thymus, lungs, and heart were removed in order. The heart was cut at the attachments of the large vessels, the chambers opened and the clots removed.

The abdominal cavity was next opened and the liver, spleen, pancreas, testes (in the males), bladder, stomach with intestines, ovaries (in the females), suprarenals, and kidneys were removed in order. To prevent evaporation the abdominal cavity was kept closed with a pair of forceps as each organ was cleaned.

The body was then put into a moist chamber. The stomach and intestines were weighed, opened, and cleaned under running water. The excess water was removed with filter-paper and the canal again weighed empty. The stomach was cut off just below the pyloric sphincter and put into the moist chamber for weighing later.

The testes were next taken one at a time. The epididymides with the fat were dissected off under water and the testes were put back into the moist chamber. The fat was next dissected off the epididymides, care being taken to preserve the cauda epididymidis, which is embedded in the fat.

The body was now taken and the integument together with appendages removed and put back into the moist chamber. The vertebral canal was then opened dorsally and the spinal cord removed. The cord was detached at the caudal end and was lifted with a pair of forceps. Gentle traction was used and the spinal nerves cut near their attachment to the cord. The body was next cleaned by removing the fat, trachea, esophagus, large vessels, etc. Then it was weighed together with the head (musculature and skeleton) which gave the total weight of skeleton and musculature. The body was then put back into the moist chamber.

The organs were now weighed separately in a closed glass container, in order to prevent evaporation. The container was cleaned after each weighing. The smaller organs (hypophysis, thyroid, suprarenals, ovaries, and epididymis) were weighed to one-tenth milligram; the liver to one one-hundredth of a gram; and the other organs to one milligram.

The integument was next cleaned of fat and weighed. The muscle was then carefully removed from the skeleton by dissection. The skeleton together with the ligaments ('ligamentous skeleton') was then weighed. This weight subtracted from the total weight of muscle and skeleton gave the weight of the musculature.

The autopsy records were kept on printed record cards similar to those used by Dr. C. M. Jackson in his work on albino rats.

OBSERVATIONS

Growth of the body as a whole (chart 1)

Birth weight. The average birth weight observed in 59 cases of the present series was 79.3 grams. Of these, the 32 males averaged 77.2 grams, with a range of 51 to 132 grams. The 27 females averaged 81.8 grams, range 52 to 135 grams. Minot ('91) in a larger series found an average of 70.8 grams for 200 males (range 35 to 128 grams) and 70.1 grams for 172 females (range 35 to 111 grams). Payton and Goodall ('04) noted an average birth weight of 80 grams (57 to 120 grams) in 17 animals. Read ('12) observed an average of 76.6 grams in 15 males, and 68 grams in 13 females. From the foregoing, we may conclude that the average birth weight is between 75 and 80 grams. There is a tremendous individual variation, which, as Minot ('91) has demonstrated, depends chiefly upon the size of the litter. It appears doubtful whether there is any significant sex difference in birth weight.

Postnatal loss in body weight. There is usually a slight loss in the initial birth weight. In the present series, the average loss in one day in the 32 males was 1.4 grams, and in the 27 females 1 gram. This loss is usually recovered by the second day, the average weight for both sexes in our series being then greater than the birth weight.

The accompanying table shows the average weights by sexes for the first three days for the present series, in comparison with those observed by Minot ('91) and Read ('12).

Observations on postnatal loss in weight of guinea-pigs. Average body weight on successive days

	0 DAYS		1 DAY		2 DAYS		3 DAYS	
	Number of observations	Average weight	Number of observations	Average weight	Number of observations	Average weight	Number of observations	Average weight
Present series								
		grams		*grams*		*grams*		*grams*
Males	32	77.2	32	75.8	32	79.2	32	84.3
Females	27	81.8	27	80.8	27	84.2	27	89.2
Data from Minot ('91)								
Males	200	70.8	47	68.9	43	70.0	48	73.4
Females	172	70.1	53	72.0	53	73.8	54	77.6
Data from Read ('12)								
Males	15	76.6	15	75.0	15	76.6	15	79.8
Females	13	68.0	13	71.3	13	75.0	13	76.7

Minot found an average loss of 1.9 grams on the first day in the males, 1.1 grams of which was recovered on the second day, the birth weight being surpassed on the third day. In the females, there was no loss in average weight, although growth was retarded in the first two days. Read found for the males an average loss of 1.6 grams on the first day, which was exactly recovered on the third day. The females (which were low in weight) made a progressive gain from the first day. We may therefore conclude that in general the loss in birth weight, though variable, is much more pronounced in the males, and is usually recovered by the second day. As observed by Minot, however, there is much individual variation in the loss and recovery. In our series, for example, nine males and nine females showed no postnatal loss in body weight. On the other hand, recovery was delayed beyond the second day in a few cases, the extreme being the fourth and fifth day in two females.

Course of postnatal growth. The further growth in body weight is shown in chart 1, which represents composite curves for each sex of the present series up to about 200 days, or 700 grams in body weight. The growth appears more rapid up to about 100 days (550 grams). Thereafter it becomes slower, increasing only about 150 grams in the next 100 days. Beyond this point (700 grams) the course of growth was not followed in the present series; but the postnatal growth curve evidently presents three phases: 1) a period of initial loss; 2) a period of rapid growth; 3) a period of slower growth as the adult stage is approached.

Among the adults (of unknown age) autopsied in the present series, two females exceeded 1100 grams in body weight. Minot observed an average of about 800 grams reached in a year. As shown by the curves in chart 1, it is evident that in average growth his animals were somewhat behind ours, requiring about 300 days to reach the body weight of ours at 200 days. Lantz ('18) says: "A full-grown cavy in good flesh should weigh nearly 2 pounds. This weight will not often be attained under 18 months of age. Instances of 3 pounds weight for males at 3 years have been recorded. As a rule females, except when pregnant, are lighter than males of the same age."

The sex differences in postnatal growth are shown by the curves in chart 1. The number of observations for each sex upon which the curves are based for the present series is shown in the following table.

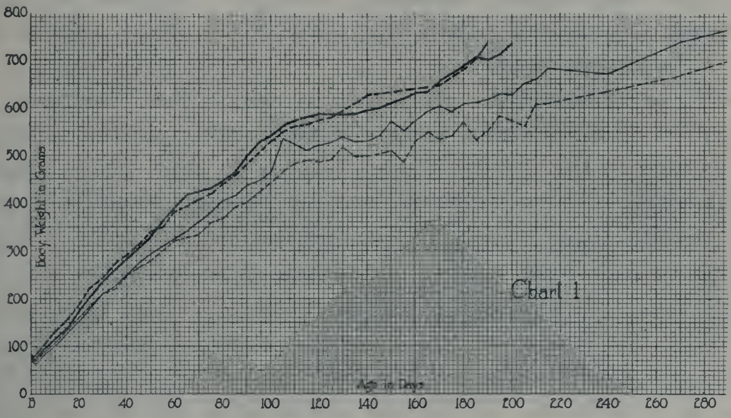
Number of observations on body weight at various ages

	AGE IN DAYS									
	0	15	30	45	60	75	90	110	140	170
Males	32	28	24	23	12	8	8	6	3	3
Females	27	25	25	17	12	9	9	5	4	1

On account of individual variations, it is evident that the number of observations beyond two months of age in our series is too small to be significant. As shown by the curves, however, it appears that the females slightly surpass the males in average weight up to about fifty-two days of age; thereafter the males average heavier for a while. The heaviest adults observed were females, which is evidence that they again surpass the males at some (undetermined) point.

In the following charts the data are plotted against body weight in each case except in chart 1, in which average body weight is plotted against age. Formulas for the various growth curves have been given in the text.

In charts 2 to 25 the individual males are represented by the solid black circles, females by the open circles, and the averages (usually for each 100 grams of body weight) by the encircled crosses. Lazareff's ('95) data, where available, are entered as black squares (males) for comparison, but are not included in the averages for the curves.



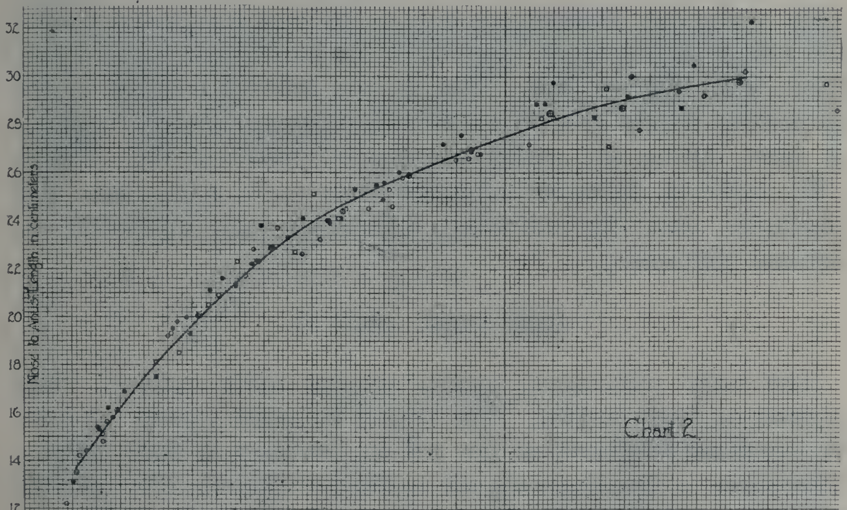


Chart 1 Growth curve for body weight in grams, plotted against age in days. The heavier lines represent the growth of the present series; the solid line for the males, the broken line for the females. The lighter lines similarly represent the growth curves as based upon the data of Minot ('91).

Chart 2 Growth curve for the nose-anus length in centimeters, plotted against body weight in grams.

As to sex differences in postnatal growth of guinea-pigs, Minot ('91) concludes: "The females therefore are at birth slightly smaller than the males, during the first month decidedly larger, during the remainder of the first year considerably smaller, but when adult again decidedly heavier." Curves for each sex, based upon Minot's data (up to 300 days) are also shown on chart 1 for comparison.

Growth of individuals. In order to study the variations in the growth of individuals, growth curves were plotted (though not included in the present paper) for about sixty cases, beginning at birth. These were followed for various periods, but only a few beyond three months, and none beyond 200 days. When the various individual curves are placed upon a single chart for examination, two conclusions are apparent: 1) There are marked individual variations in the growth curves, although not so marked as the differences in birth weight, and becoming relatively less as age progresses. 2) Within the limits of the age examined, while temporary fluctuations tend to become readjusted during the course of growth, in most cases the individuals tend to preserve their relative size. That is, the relative position as regards body weight at birth will usually be approximately retained, at least during the earlier months of postnatal life. Minot ('91), however, followed individual cases up to a later age, and concluded that the individual differences tend ultimately to become obliterated.

Body length (chart 2)

The body (nose-anus) length appears quite constant when plotted on body weight. The length increases rapidly at first, and gradually falls off as the animal increases in body weight. The curve is therefore convex upward. The formula for this curve of growth in body length is:

$$Y = ax + b - cx^2$$

Y = body length in cm.; x = body weight in grams

$$\left.\begin{array}{l} a = 0.0481 \\ b = 10.45 \\ c = 0.000036 \end{array}\right\} \text{From birth to 500 grams body weight}$$

$$\left.\begin{array}{l} a = 0.024 \\ b = 16.0 \\ c = 0.00001 \end{array}\right\} \text{From 500 to 1000 grams body weight}$$

Head weight (chart 3)

The head plotted against body weight for sexes combined forms almost a straight line. It is interesting to note, however, that the head of the males becomes slightly but distinctly heavier than that of the females of the same body weight. In the upper part, therefore, there should be separate curves for each sex. At a body weight of about 700 grams, the head of the male averages about 14 per cent heavier than that of the female, as shown in chart.

This characteristic is especially noticeable in older and larger adult guinea-pigs, in which the head appears relatively much larger in the males. The formula for the curve of growth in head weight (sexes combined) is:

$Y = ax + b$
Y = head weight in grams
X = body weight in grams
$a = 0.104$
$b = 7.8$

Integument (chart 4)

The growth in weight of the integument from birth to 700 grams body weight appears to be almost directly proportional to that of the body as a whole. The growth curve therefore forms nearly a straight line. Beyond 700 grams body weight, the integument fails to increase proportionally to the body weight. At the upper end of the curve, the integument of the males appears to be somewhat heavier than that of females. The formula for the curve is:

$Y = ax + b$
Y = integument weight in grams
X = body weight in grams
$a = 0.167$
$b = 1.4$

This formula is good from birth to a body weight of about 800 grams.

Ligamentous skeleton (*chart 5*)

The growth curve for the moist skeleton (including ligaments) forms nearly a straight line. There is some indication of a sex difference at the upper end of the curve, the male skeleton appearing relatively heavier. The formula for the growth in weight of the ligamentous skeleton is:

$Y = ax + b$
Y = skeleton weight in grams
X = body weight in grams
$a = 0.068$
$b = 3.6$

This formula is good from birth to 1000 grams body weight.

Musculature (*chart 6*)

The curve of growth of the skeletal musculature presents a nearly straight line up to about 700 grams of body weight. Beyond this the musculature increases less rapidly than the body weight, so that the upper end of the curve is convex upward. A sex difference at the upper end is slight, but distinct: the musculature being relatively heavier in the males. The formulas for the weight of the musculature (sexes combined) are as follows:

Chart 3 Growth curve for the head weight in grams plotted against body weight in grams. Although the averages are for males and females combined, there is an apparent sex difference, the male heads appearing heavier than the female heads in the upper half of the series.

Chart 4 Growth curve for the weight of the integument in grams, plotted against body weight in grams. The integument for the male appears heavier than that for the female in the upper part of the series, but the sexes are combined in calculating the formula.

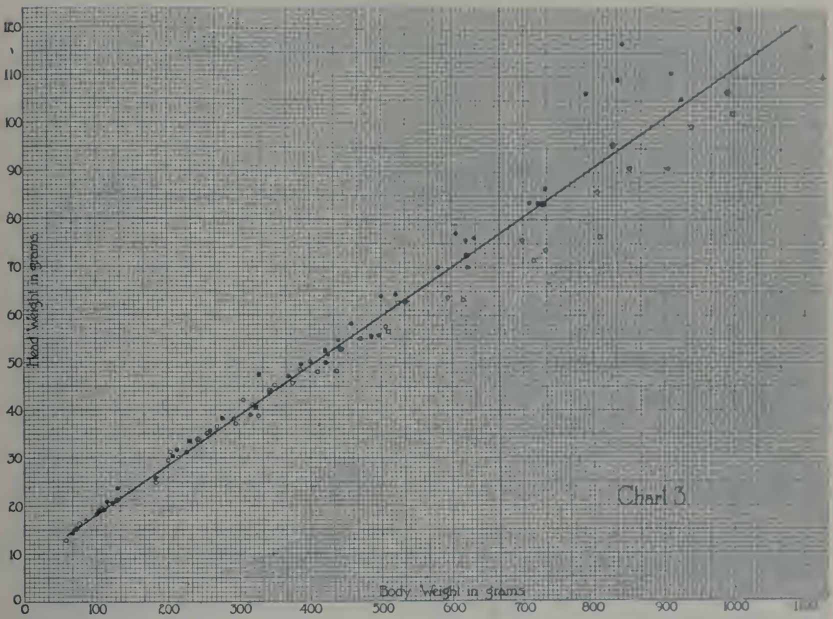


Chart 3

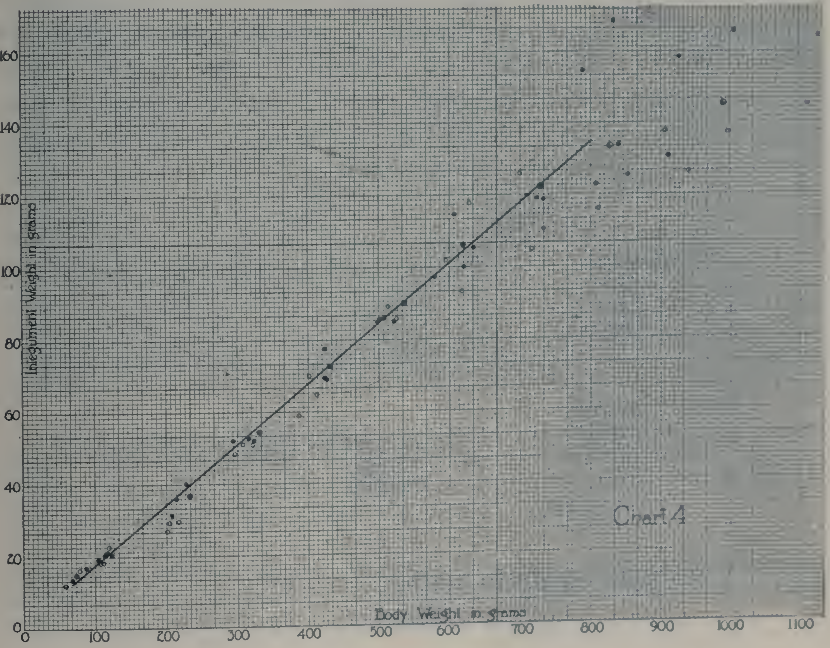


Chart 4

$$\left.\begin{array}{l} Y = ax - b \\ a = 0.393 \\ b = 7.3 \end{array}\right\} \text{From 70 to 700 grams body weight}$$

$$\left.\begin{array}{l} Y = ax - b - cx^2 \\ a = 0.64 \\ b = 57.5 \\ c = 0.00025 \end{array}\right\} \text{From 700 to 1000 grams body weight}$$

Y = weight of musculature in grams
X = body weight in grams

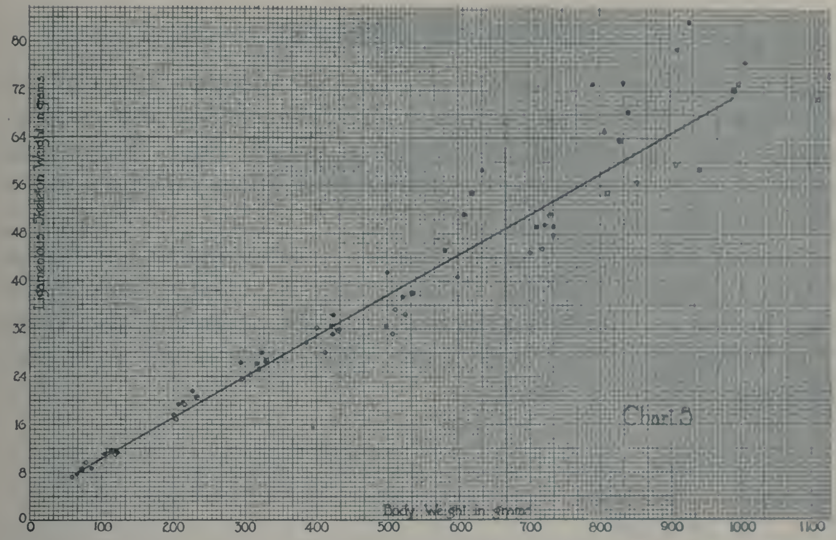
Brain (chart 7)

The field graph of the brain shows a surprisingly large variation in the individual weights. The approximate average curve of growth rises rapidly in the earlier phase, gradually slowing as the weight of the guinea-pig increases. The weights found by Lazareff ('95) in his ten normal guinea-pigs have been included (squares), and they fit in very well with the present observations. There is no marked sex difference in the weight of the brain, although that of the male appears slightly heavier in the older animals. The formulas for the growth in brain weight (sexes combined) are as follows:

$$\left.\begin{array}{l} Y = ax + b - cx^2 \\ a = 0.0089 \\ b = 1.74 \\ c = 0.000011 \end{array}\right\} \text{From birth to 300 grams body weight}$$

$$\left.\begin{array}{l} \text{Same formula} \\ a = 0.0027 \\ b = 2.70 \\ c = 0.000001 \end{array}\right\} \text{From 300 to 1000 grams body weight}$$

Y = brain weight in grams
X = body weight in grams



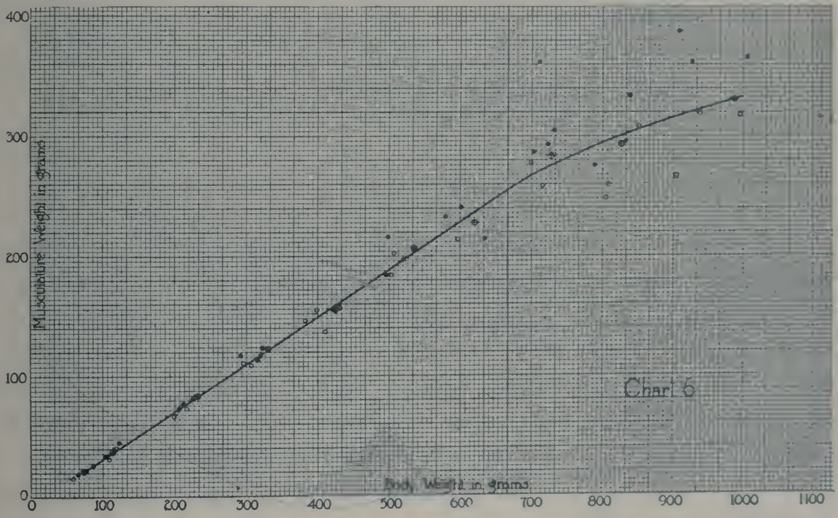


Chart 5 Growth curve for the weight of the ligamentous skeleton in grams, plotted against body weight in grams. The male skeleton usually appears slightly higher than that of the female at the same body weight, although the sexes are combined for the averages and curve.

Chart 6 Growth curve for the weight of the musculature in grams, plotted against body weight in grams. Here also there is an apparent sex difference, the male musculature appearing heavier than the female in the upper part of the series, although the sexes are combined for the averages and curve.

Spinal cord (chart 8)

The spinal-cord weight appears far less variable than that of the brain. The curve of growth for the cord is less convex upward, and more nearly approaches a straight line. There is a slight early rise which very gradually slows down with no apparent sex difference.

Lazareff's data are included (squares). They appear somewhat higher than ours, although the difference is not very great. It may be due to difference in technique in the removal of the cord. The formula for the growth of the spinal cord, based upon our own data only, is as follows:

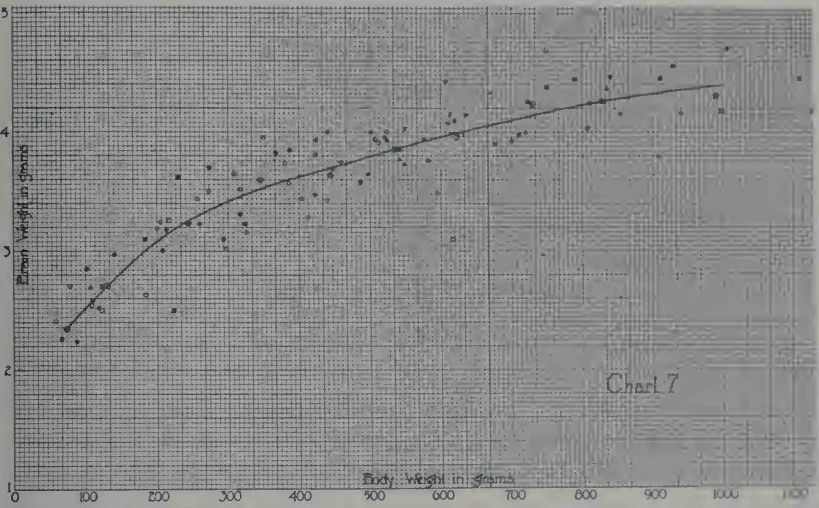
$$\begin{aligned} Y &= ax + b - cx^2 \\ a &= 0.00215 \\ b &= 0.138 \\ c &= 0.0000008 \end{aligned}$$

Y = spinal cord weight in grams
X = body weight in grams

Eyeballs (chart 9)

In man and other mammals the growth curve for the eyeballs resembles that of the brain, growth being completed at a relatively early period. In the guinea-pig, however, this is apparently true only up to 500 or 600 grams of body weight. Thereafter an acceleration of growth occurs which appears to continue throughout the rest of the growth period, resulting in a biphased curve. The cause of this late acceleration of growth in the eyeballs is not clear. The formulas for the growth in weight of the eyeballs are as follows:

$$\left.\begin{aligned} Y &= ax + b - cx^2 \\ a &= 0.00195 \\ b &= 0.31 \\ c &= 0.00000175 \end{aligned}\right\} \text{From birth to 500 grams body weight}$$



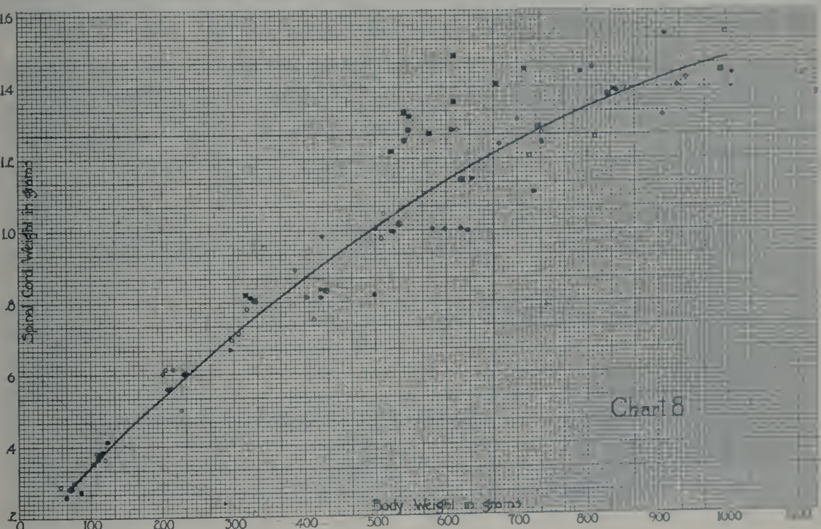


Chart 7 Growth curve for the weight of the brain in grams, plotted against body weight in grams. Lazareff's cases (squares) fit in perfectly with the present series. The individual variation in the brain weight is greater than might be expected.

Chart 8 Growth curve for the weight of the spinal cord in grams, plotted against body weight in grams. Lazareff's cases (squares) average higher than the present series.

$$\left.\begin{array}{lcl} Y &=& cx^2 + b - ax \\ a &=& 0.0004 \\ b &=& 0.80 \\ c &=& 0.000001 \end{array}\right\} \text{From 500 to 1000 grams body weight}$$

Y = weight of the eyeballs in grams
X = body weight in grams

Hypophysis (chart 10)

The hypophysis (pituitary gland) also shows a biphased growth curve. There is a phase of rapid growth in the earlier part of the curve which slows down as age advances. This is followed by an acceleration of growth beginning at about 400 grams of body weight. The weights of the individual glands show a relatively large variation, especially after the guinea-pig exceeds 300 grams in body weight. There is no apparent sex difference in weight. Richet's ('98) averages for the weight of the hypophysis in the guinea-pig run somewhat below the present series, except at a body weight of about 500 grams. The formulas for growth in the weight of the hypophysis are as follows:

$$\left.\begin{array}{lcl} Y &=& ax + b - cx^2 \\ a &=& 0.0000343 \\ b &=& 0.0017 \\ c &=& 0.000000026 \end{array}\right\} \text{From birth to 400 grams body weight}$$

$$\left.\begin{array}{lcl} Y &=& ax + b + cx^2 \\ a &=& 0.0000021 \\ b &=& 0.008 \\ c &=& 0.000000015 \end{array}\right\} \text{From 400 to 1000 grams body weight}$$

Y = weight of hypophysis in grams
X = body weight in grams

Chart 9 Growth curve for the weight of the eyeballs in grams, plotted against body weight in grams. The curve of average growth is biphased.

Chart 10 Growth curve for the weight of the hypophysis in grams, plotted against body weight in grams. The curve is biphased and there is great individual variation, but no apparent sex difference.

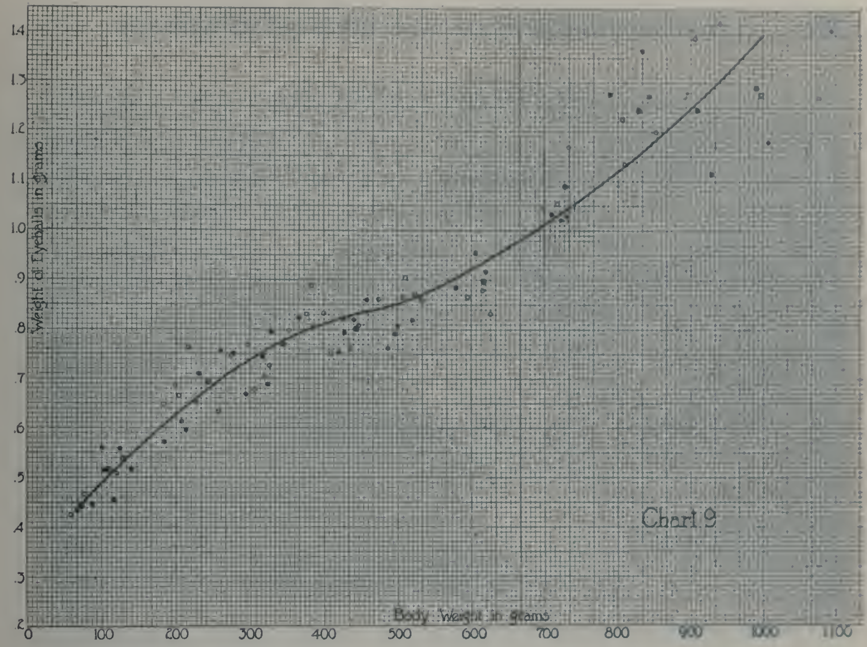


Chart 9

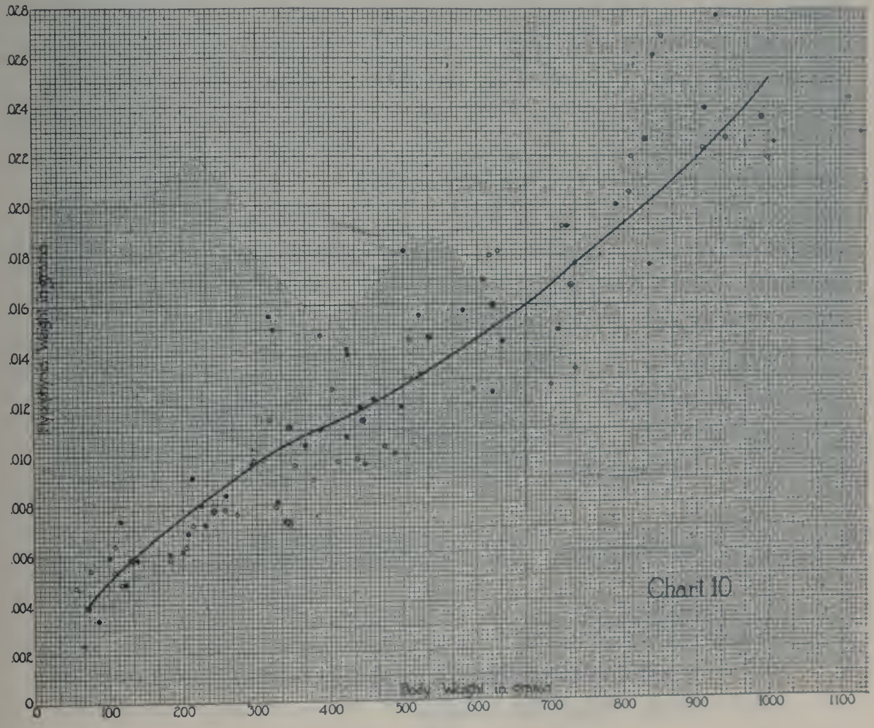


Chart 10

Thyroid gland (*chart 11*)

The average growth in weight of the thyroid gland forms nearly a straight line. There is clearly a great individual variation, especially in the older animals. There is no apparent sex difference in the weight of the thyroid gland. McCarrison's ('21) average at a body weight of about 521 grams is about 40 per cent below our calculated average. The formula for the growth in weight of the thyroid gland is as follows:

$Y = ax + b$
Y = weight of thyroid gland in grams
X = body weight in grams
$a = 0.00014$
$b = 0.008$

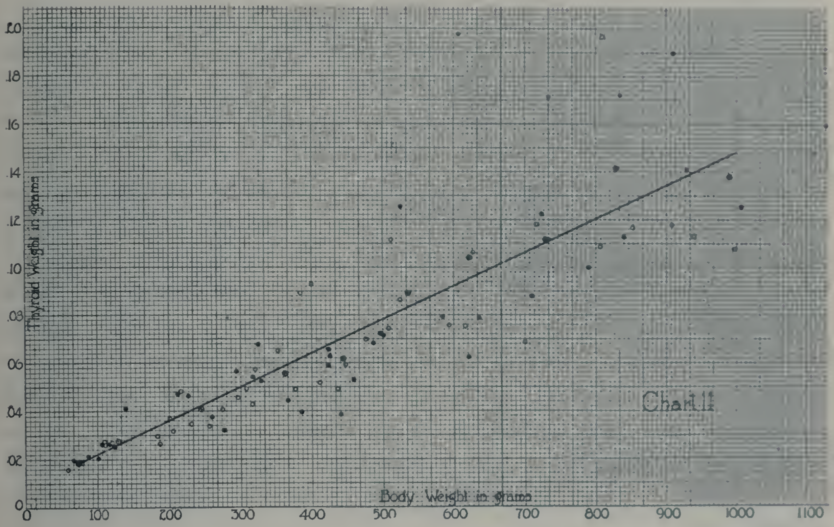
Suprarenal gland (*chart 12*)

The suprarenal glands plotted on body weight show a biphased curve. Up to about 400 grams body weight the curve is slightly convex upward. Then the growth curve shows a remarkable rise to the end of the series. There is no sex difference, but a considerable individual variation in weight. Richet's ('98) averages for the weight of the suprarenals in the guinea-pig check fairly closely with the present series. However, McCarrison ('21) found an average weight for the suprarenals at a body weight of 521 grams, which is 90 per cent above our calculated average. The formulas for the growth curve in weight of the suprarenal glands are as follows:

$$\left.\begin{array}{l} Y = ax - b - cx^2 \\ a = 0.00083 \\ b = 0.035 \\ c = 0.00000084 \end{array}\right\} \text{From birth to 400 grams body weight}$$

$$\left.\begin{array}{l} Y = cx^2 + b - ax \\ a = 0.00069 \\ b = 0.214 \\ c = 0.0000014 \end{array}\right\} \text{From 400 to 1000 grams body weight}$$

Y = weight of suprarenals in grams
X = body weight in grams



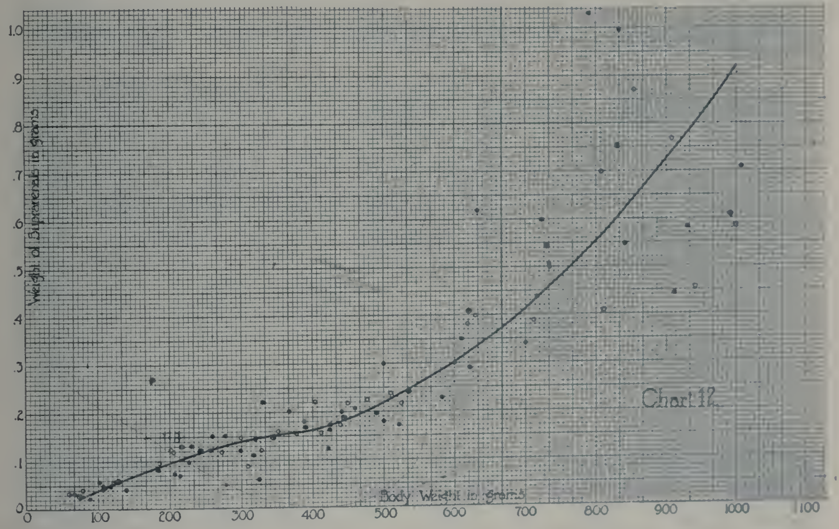


Chart 11 Growth curve for the weight of the thyroid gland in grams, plotted against body weight in grams. There is marked individual variation, especially in the upper half of the series.

Chart 12 Growth curve (biphased) for the weight of the suprarenal glands in grams, plotted against body weight in grams. Individual variation is marked in the upper half of the series, but no sex difference is apparent.

Heart (chart 13)

The heart from birth to about 700 grams of body weight apparently grows directly in proportion to the body weight. Beyond 700 grams the heart weight lags behind slightly. The average weights form nearly a straight line, with a convexity upward at the upper end of the curve. There is little individual variation and no apparent sex difference. Lazareff's ('95) weights are plotted (squares), and fit in well with the present observations. McCarrison's ('21) normal average for the heart at a body weight of 521 grams is 50 per cent above our calculated average. Similarly Joseph's ('08) thirty-three females averaging 257 grams and fourteen males averaging 384 grams have heart weights 30 per cent and 50 per cent higher, respectively. It is difficult to account for these apparent differences in normal heart weight. The formulas for the growth in heart weight are as follows:

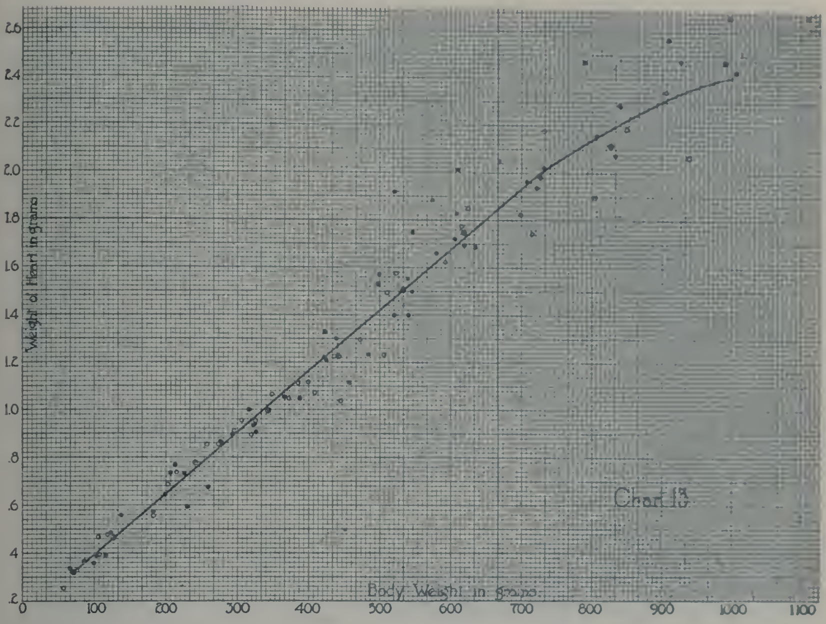
$$\left.\begin{array}{l} Y = ax + b \\ a = 0.00256 \\ b = 0.134 \end{array}\right\} \text{From birth to 700 grams body weight}$$

$$\left.\begin{array}{l} Y = ax - b - cx^2 \\ a = 0.00585 \\ b = 0.94 \\ c = 0.0000025 \end{array}\right\} \text{From 700 to 1000 grams body weight}$$

Y = heart weight in grams
X = body weight in grams

Spleen (chart 14)

The spleen is greatly variable in weight, as is the case in other animals, including man. The average growth forms a biphased curve which is convex upward for the first 300 grams of body weight and convex downward beyond this point. It will be noted that in the upper half of the curve nearly all of the female entries are above the curve, and nearly all the males below, suggesting a sex difference (of doubtful significance). Lazareff's ('95) weights for the spleen (plotted as squares) are somewhat



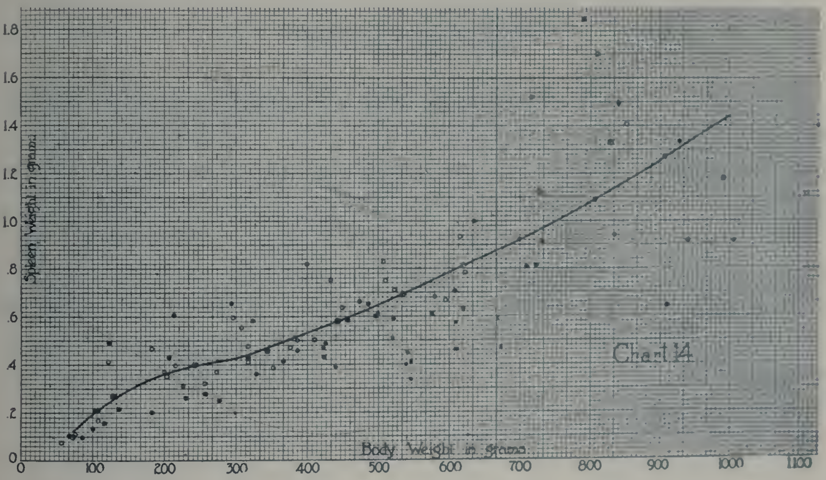


Chart 13 Growth curve (biphased) for the weight of the heart in grams, plotted against body weight in grams. Lazareff's data (squares) fit in fairly well with the present series, but show greater individual variation.

Chart 14 Growth curve for the weight of the spleen in grams, plotted against body weight in grams. Individual variation is great. Lazareff's data (squares) average lower than the present series.

lower than the observations in this series. Richet's ('98) are also lower, corresponding to Lazareff's weights, but McCarrison's ('21) normal average at 521 grams body weight agrees closely with the present series. The formulas for the growth in weight spleen are as follows:

$$\left.\begin{aligned} Y &= ax - b - cx^2\\ a &= 0.0032\\ b &= 0.08\\ c &= 0.000005 \end{aligned}\right\}\text{From 100 to 300 grams body weight}$$

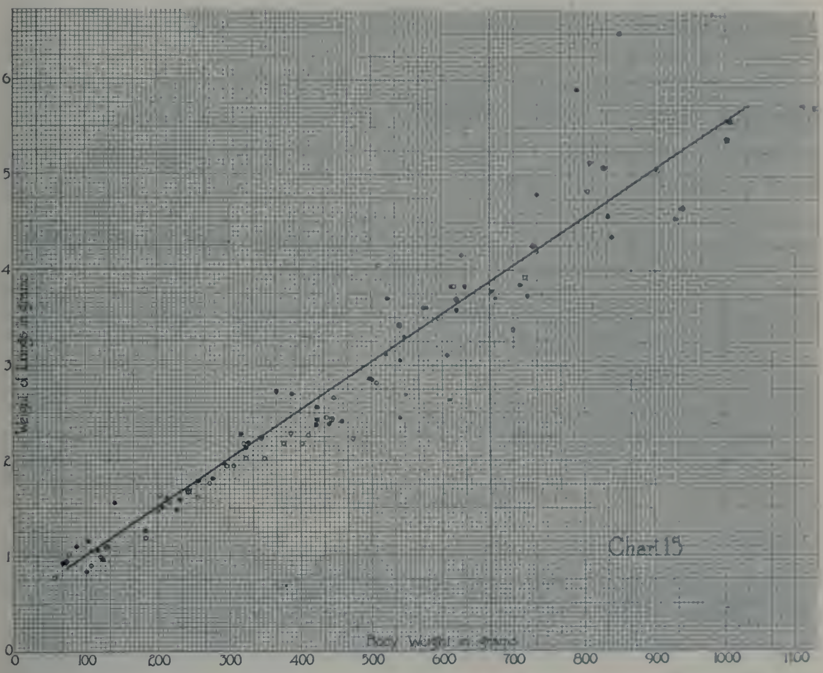
$$\left.\begin{aligned} Y &= ax + b + cx^2\\ a &= 0.00054\\ b &= 0.205\\ c &= 0.0000007 \end{aligned}\right\}\text{From 300 to 1000 grams body weight}$$

Y = spleen weight in grams
X = body weight in grams

Lungs (chart 15)

The lungs present an even growth in weight, with but slight individual variations, especially in the lower part of the curve. Two cases showing areas of consolidation were excluded as abnormal. The average forms an almost perfectly straight line. There is no apparent sex difference in weight. Lazareff's ('95) weights are inserted (squares) and fit in perfectly with the others. McCarrison's ('21) normal average at 521 grams body weight is 70 per cent higher than our calculated average, and may possibly have been due to infection. The formula for growth in weight of the lungs is as follows:

$Y = ax + b$
Y = weight of lungs in grams
X = body weight in grams
$a = 0.0051$
$b = 0.49$



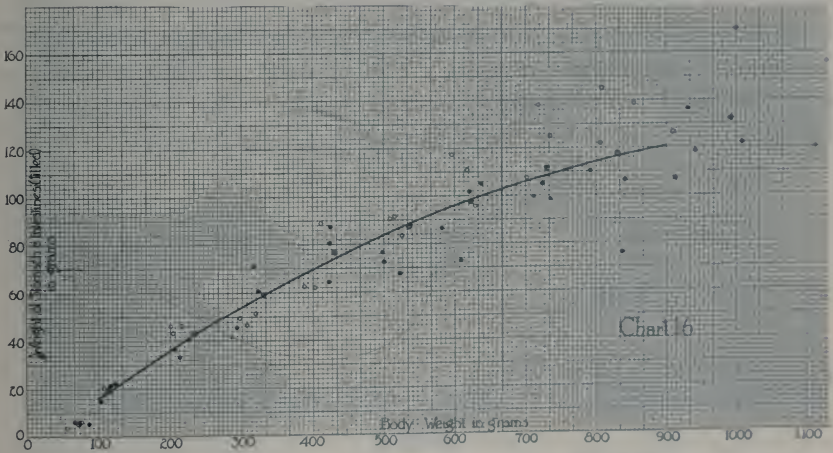


Chart 15 Growth curve for the weight of the lungs in grams, plotted against body weight in grams. Lazareff's data (squares) fit in perfectly with the present series.

Chart 16 Growth curve (biphased) for the weight of the stomach and intestines (with contents) plotted against body weight in grams. The individual variation is not so large as might be expected.

Stomach and intestines with contents (chart 16)

The curve of average growth in weight for the canal with contents shows a slight convexity upward, with less individual variation than might be expected. The formula for the canal with contents is as follows:

$Y = ax - b - cx^2$ (Good only from 100 to 900 grams body weight

Y = weight of stomach and intestines (filled) in grams
X = body weight in grams
a = 0.23
b = 6.0
c = 0.0001

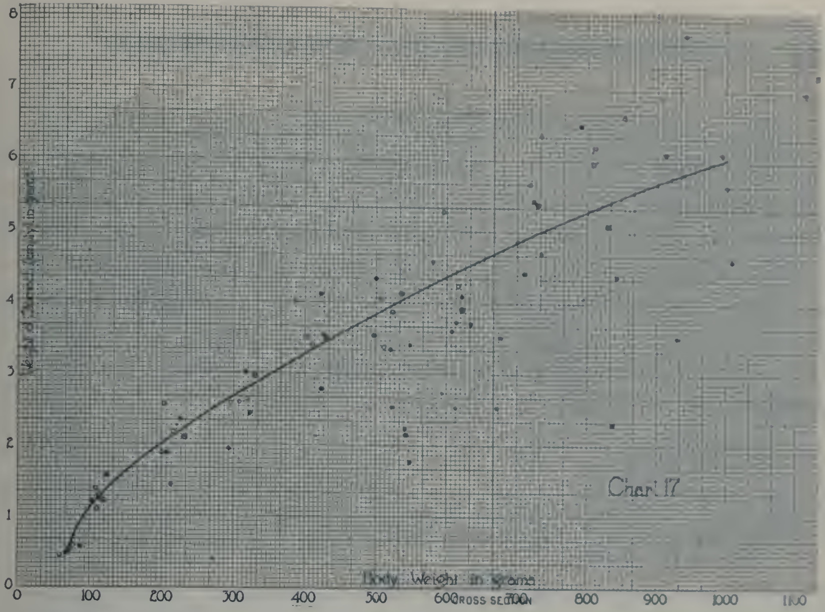
Stomach (chart 17)

The average weight of the empty stomach gives a curve similar to that of the filled stomach and intestines. There is an early rapid growth followed by a gradually decreasing rate of growth. Lazareff's ('95) data are included (squares) and appear decidedly lower than the cases in the present series at corresponding body weights. This may be due to difference in technique of removal of the stomach or its contents. The mucous membrane is very easily detached unless great care is taken. The formulas for growth in weight of the empty stomach are as follows:

$$\left.\begin{aligned} Y &= ax - b - cx^2 \\ a &= 0.0262 \\ b &= 1.04 \\ c &= 0.000055 \end{aligned}\right\} \text{From birth to 200 grams body weight}$$

$$\left.\begin{aligned} Y &= ax + b - cx^2 \\ a &= 0.0077 \\ b &= 0.55 \\ c &= 0.0000022 \end{aligned}\right\} \text{From 200 to 1000 grams body weight}$$

Y = weight of empty stomach in grams
X = body weight in grams



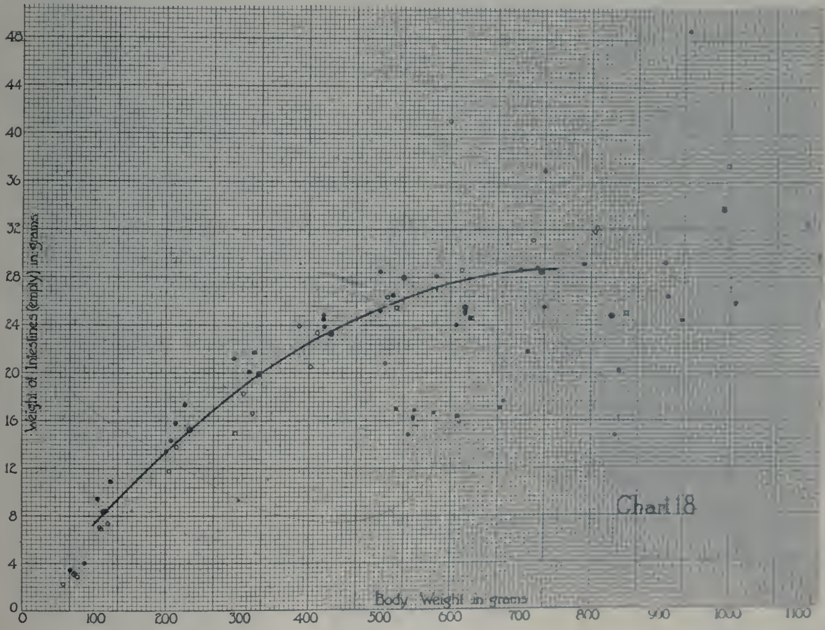


Chart 17 Growth curve for the weight of the empty stomach in grams, plotted against body weight in grams. Lazareff's observations (squares) average lower than the present series.

Chart 18 Growth curve for the weight of the empty intestines in grams, plotted against body weight in grams. Individual variation is marked in the upper part of the series. Lazareff's cases (squares) are definitely lower than the present series.

Intestines (chart 18)

The average growth in weight of the empty intestines forms a curve which is convex upward. There is a great individual variation in the upper part of the series, for which the curve is not calculated. The cases of Lazareff ('95) are plotted (squares) and are much lower than the corresponding weights in this series, as was also true of the stomach. The formula for growth in weight of the empty intestines (good only from 100 to 750 grams of body weight) is as follows:

$Y = ax + b - cx^2$
$a = 0.0761$
$b = 0.3$
$c = 0.000051$
Y = weight of empty intestines in grams
X = body weight in grams

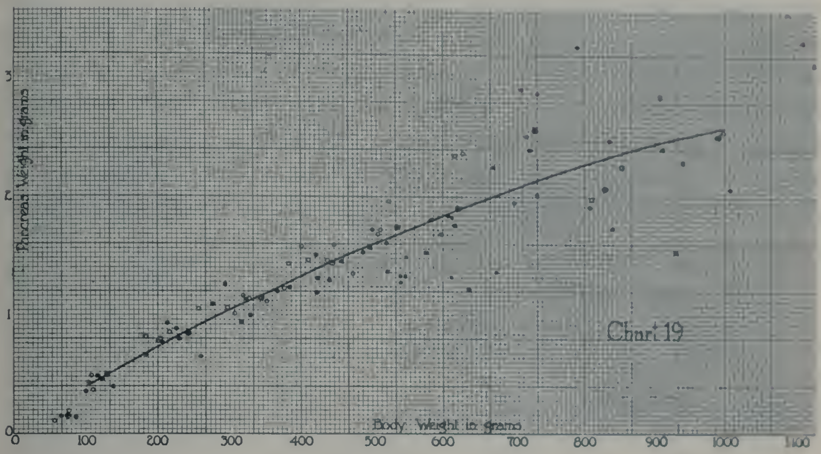
Pancreas (chart 19)

The weights of the pancreas show a curve in general like those of the alimentary canal, with but very little individual variation in the lower half of the curve. Lazareff's ('95) weights are included (squares), and average somewhat below the cases in the present series. Richet's ('98) averages check closely with ours. The formula for growth in weight of the pancreas is as follows:

(Good only from 100 to 1000 grams of body weight)
$Y = ax + b - cx^2$
$a = 0.00365$
$b = 0.045$
$c = 0.00000109$
Y = pancreas weight in grams
X = body weight in grams

Liver (chart 20)

The growth in weight of the liver is in direct proportion to the body weight, thus giving a straight line from birth to about 800 grams of body weight. The individual variations are large in



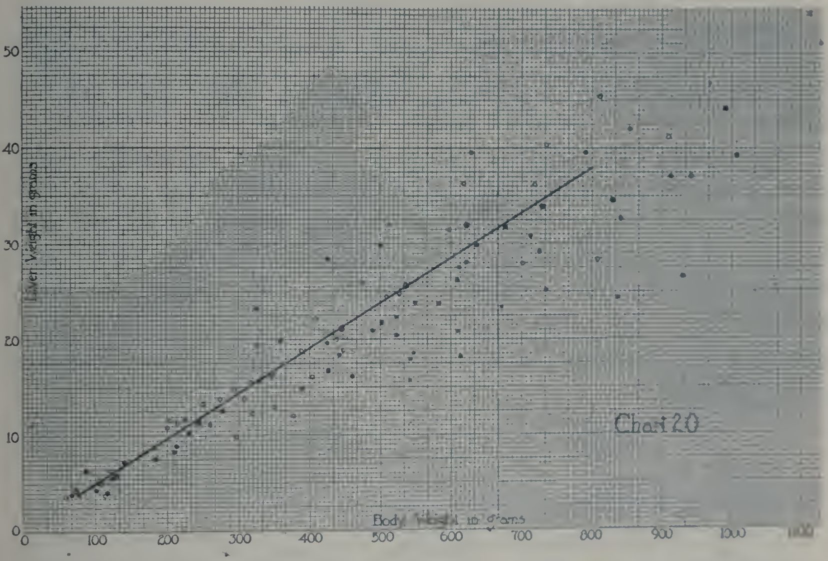


Chart 19 Growth curve for the weight of the pancreas in grams, plotted against body weight in grams. In the upper half of the series there is marked individual variation in weight. Lazareff's data (squares) fit in fairly well with the present series.

Chart 20 Growth curve for the weight of the liver in grams, plotted against body weight in grams. Lazareff's cases (squares) fit in fairly well with the present series.

the upper half of the series. No sex difference is shown. Lazareff's ('95) data (squares) average slightly lower than the cases in this series. Richet's ('98) data also average slightly lower, and McCarrison's ('21) average at 521 grams body weight is about 20 per cent below our curve. The liver is an organ notably variable in weight, and especially influenced by differences in diet. The formula for growth in weight of the liver is as follows:

(Good from birth to 800 grams of body weight)
$Y = ax + b$
Y = liver weight in grams
X = body weight in grams
$a = 0.047$
$b = 0.35$

Kidneys (chart 21)

The average weights of the kidneys show a curve with a slight increase in the earlier period. Beyond a body weight of 100 grams, they form a nearly straight line throughout the remainder of the series. Individual variation is slight. Lazareff's ('95) data (squares) fit in perfectly with the present series. McCarrison's ('21) average at 521 grams of body weight is 40 per cent higher and corresponds to the averages of Richet ('98), who weighed the kidney with the capsule. This would not fully account for the differences, however. No sex difference is shown. The formula for the growth in weight of the kidneys is as follows:

(Not good for body weight below 100 grams)
$Y = ax + b$
Y = kidney weight in grams
X = body weight in grams
$a = 0.0063$
$b = 0.50$

Chart 21 Growth curve for the weight of the kidneys in grams, plotted against body weight in grams. Lazareff's cases (squares) fit in perfectly with the present series.

Chart 22 Growth curve (biphased) for the weight of the urinary bladder in grams, plotted against body weight in grams. There is marked individual variation in weight. Lazareff's data (squares) fit in well with the present series.

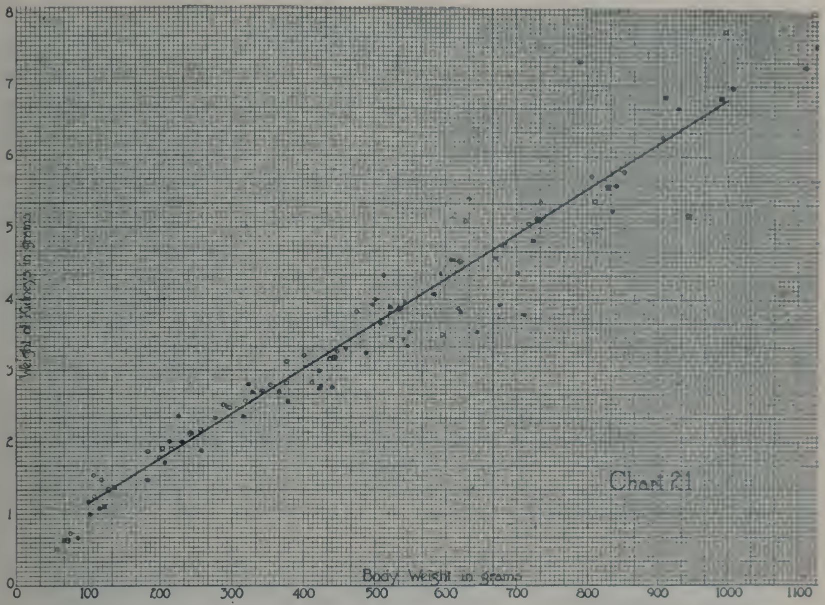


Chart 21

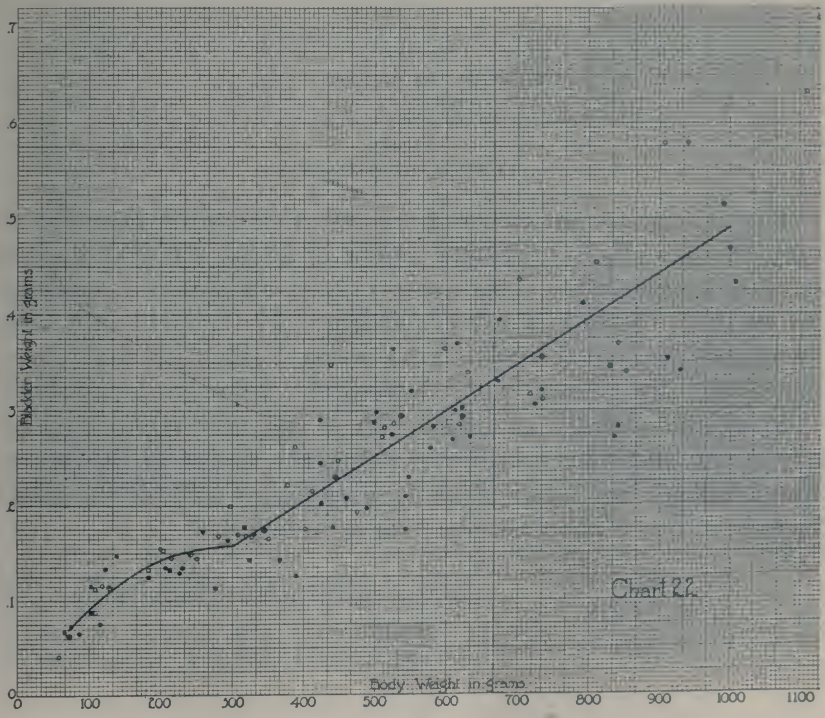


Chart 22

Urinary bladder (chart 22)

The curve of average weight of the empty urinary bladder presents a rapid rise up to about 150 grams in body weight. Then it ascends less steeply up to about 300 grams in body weight. Finally it rises steadily upward, forming nearly a straight line of growth to the end of the series. There is a large individual variation, especially in guinea-pigs above 300 grams in body weight. No sex difference is shown. Lazareff's ('95) data (squares) fit in perfectly with the present series. The formulas for growth in weight of the bladder are as follows:

$$\left.\begin{array}{l} Y = ax - b - cx^2 \\ a = 0.00113 \\ b = 0.002 \\ c = 0.000002 \end{array}\right\} \text{From birth to 300 grams body weight}$$

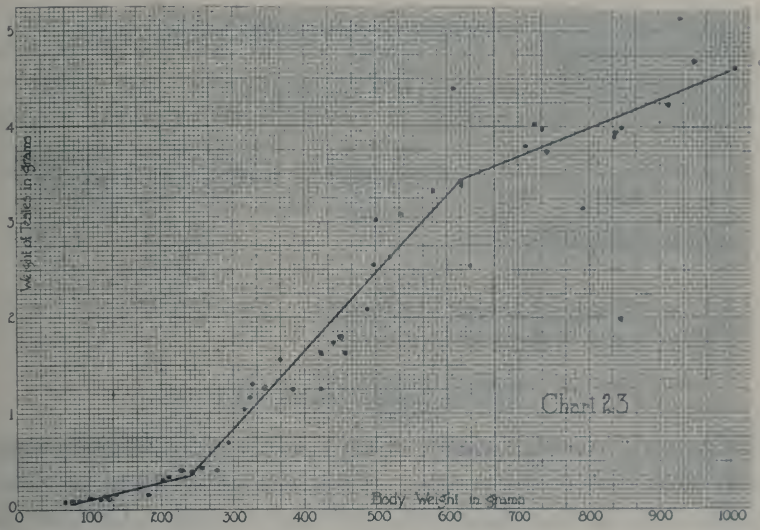
$$\left.\begin{array}{l} Y = ax + b \\ a = 0.00048 \\ b = 0.013 \end{array}\right\} \text{From 300 to 1000 grams body weight}$$

Y = weight of bladder in grams
X = body weight in grams

Testes (chart 23)

The average weight curve of the testes shows first a phase of very slow growth up to a body weight of about 250 grams when it takes its first rise. This rise continues somewhat irregularly up to about 600 grams in body weight. The growth rate then becomes slower to the end of the series. The data show comparatively little individual variation throughout. Richet's ('98) weights average about one-half of the weight indicated by our curve, and may possibly represent the weight of one testis. For simplicity the formulas for the growth in weight of the testes have been based upon a zig-zag curve as follows:

$$\left.\begin{array}{l} Y = ax - b \\ a = 0.0018 \\ b = 0.08 \end{array}\right\} \text{From birth to 240 grams body weight}$$



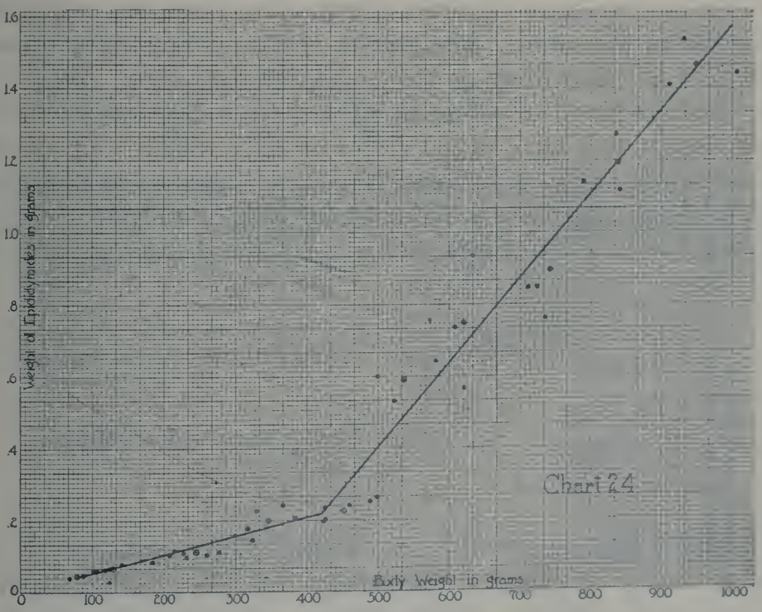


Chart 23 Growth curve for the weight of the testes in grams, plotted against body weight in grams. The growth is complicated, being represented by a triphased curve.

Chart 24 Growth curve (biphased) for the weight of the epididymides in grams, plotted against body weight in grams.

$$\left.\begin{aligned} Y &= ax - b \\ a &= 0.00815 \\ b &= 1.60 \end{aligned}\right\} \text{From 240 to 620 grams body weight}$$

$$\left.\begin{aligned} Y &= ax + b \\ a &= 0.003 \\ b &= 1.59 \end{aligned}\right\} \text{From 620 to 1000 grams body weight}$$

Y = weight of testes in grams
X = body weight in grams

Epididymides (chart 24)

The graph of average weight of the epididymides appears much simpler than that of the testes. It has the same initial period of slow growth, but extending over a longer period. The marked rise starts at the body weight of about 400 grams, and continues to the end of the series. The growth of the epididymides apparently does not slow down as soon as that of the testes. Payton's ('05) averages for the combined weight of testes and epididymides check closely with ours at 252 grams of body weight, but are 33 per cent lower at 152 grams and 10 per cent higher at 322 grams of body weight when compared with our calculated curves. The formulas for growth in weight of the epididymides are as follows:

$$Y = ax - b$$

$$\left.\begin{aligned} a &= 0.00053 \\ b &= 0.003 \end{aligned}\right\} \text{From birth to 420 grams body weight}$$

$$\left.\begin{aligned} a &= 0.00235 \\ b &= 0.767 \end{aligned}\right\} \text{From 420 to 1000 grams body weight}$$

Ovaries (chart 25)

The individual variation in the weights of the ovaries is not so great as might be expected, especially after the age of puberty. The average weight curve shows an initial phase of slow growth, which soon takes a precipitous rise between 100 and 200 grams in body weight. Then the curve ascends slowly, the average weight forming a straight line until a body weight of 700 grams is reached. Then there is a second acceleration of growth which extends to the end of the series. The individual variation is probably due to ovulation and the associated formation of corpora lutea. The formulas for the growth in weight of the ovaries are as follows:

$$\left.\begin{array}{l} Y = cx^2 + b - ax \\ a \ = 0.00033 \\ b \ = 0.014 \\ c \ = 0.0000027 \end{array}\right\} \text{From birth to 200 grams body weight}$$

$$\left.\begin{array}{l} Y = ax + b \\ a \ = 0.000072 \\ b \ = 0.042 \end{array}\right\} \text{From 200 to 700 grams body weight}$$

$$\left.\begin{array}{l} Y = ax - b \\ a \ = 0.0004 \\ b \ = 0.188 \end{array}\right\} \text{For body weight over 700 grams}$$

Y = weight of ovaries in grams
X = body weight in grams

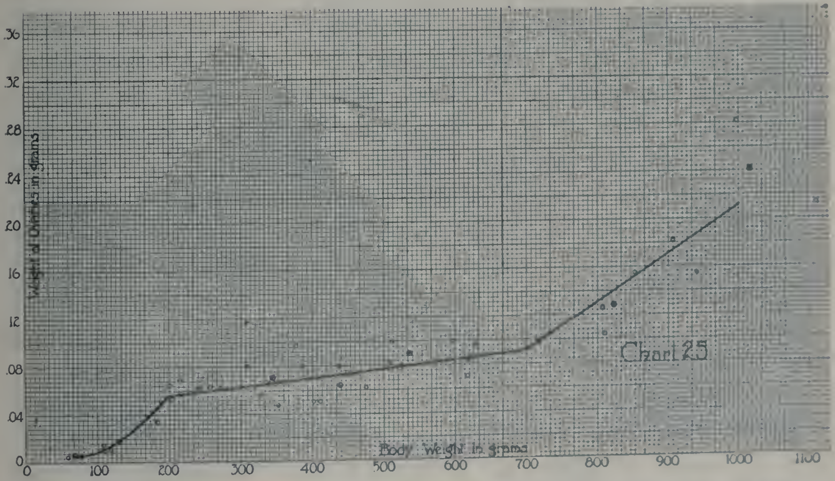


Chart 25 Growth curve for the weight of the ovaries in grams, plotted against body weight in grams. The growth is complicated, being represented by a triphased curve.

DISCUSSION

In the preceding pages, comparison has been made between our results and those of previous observers, and the principal points of agreement and difference have been noted. As to the postnatal growth in body weight, our results are in general agreement with those of Minot ('91), although differing on some minor points. Both Minot's data and our own on the birth weight and postnatal loss differ somewhat from those of Read ('12, '13). The weights recorded by Lazareff ('95) correspond rather closely with ours for the brain, heart, lungs, kidneys, bladder, pancreas, and liver. His observations on the spleen, stomach, and intestines are definitely lower, however, and those on the spinal cord are definitely higher than ours. Richet's ('98) data on the liver and pancreas fit in well with the present series, although the hypophysis and spleen average lower and the kidney (with capsule?) average higher than ours. Joseph's ('08) averages for the heart run definitely higher. Payton's ('05) averages for the epididymides and testes combined agree fairly well with ours, whereas McCarrison's averages, excepting that for the spleen, vary considerably from our data.

These discrepancies may be accounted for in various possible ways. In some cases they are probably due to an insufficient number of observations, so that accidental variations unduly affect the average. This is especially likely to happen in the case of the highly variable organs. Differences may also be due to variations in experimental error or in autopsy technique. Another factor of great importance is the dietary regime and hygienic conditions in general, which may influence markedly the growth of the body and the relative size and structure of the various parts and organs. Unsuspected pathological conditions may also influence the weights of organs. Finally there are possibly more fundamental differences, due to the race or variety of guinea-pigs used. The ordinary laboratory guinea-pigs probably represent a hybrid or mongrel stock. It would be very desirable to study the growth of the guinea-pig, including the organ weights, in a pure breed of guinea-pigs, so as to standardize this animal as has been done for the albino rat by Donaldson and his co-workers.

On account of the possible differences in apparently 'normal' guinea-pigs, it is evident that the growth norms established by the present investigation do not eliminate the necessity of providing normal controls in every experiment where this animal is used. Nevertheless it is hoped that these norms will be useful for comparison, and that they will facilitate experimental work on the guinea-pig by giving in advance an approximate idea of the course of postnatal growth in the various organs.

SUMMARY

The results of the foregoing study of growth in guinea-pigs may be summarized briefly as follows:

1. Guinea-pigs vary greatly in weight at birth, the average being about 79 grams, with a range of 51 to 135 grams in the present series. The individual birth weight is usually inversely proportional to the size of the litter. During the early growth period, individual animals seem to hold nearly the same relative position that they held at birth, heavier individuals remaining heavier, and lighter animals relatively light in weight.
2. There is usually a slight postnatal loss (average for females 1 gram; for males 1.4 grams) in body weight, which is usually recovered by the second day. After this brief initial period, there is a period of rapid growth up to about 100 days (550 grams), followed by a final period of slower growth up to maturity.
3. The females average slightly heavier than the males up to about fifty-two days of age (in the present series), after which they are surpassed by the males. However, the adult females apparently again become heavier than the males.
4. In guinea-pigs above 400 grams in body weight, the head of the male becomes relatively larger and heavier than that of the female. The skeleton, musculature, and integument also appear relatively somewhat heavier for the male in the later stages. There is a suggestion of a sex difference (of doubtful significance) in the upper part of the graphs for the body length, brain, spleen, stomach, and intestines.

5. A normal postnatal growth curve approaching a straight line is found for each of the following: head weight, integument, skeleton, musculature, thyroid gland, heart, lungs, liver, and kidneys. A curve which is convex upward represents the growth of body length, brain, spinal cord, stomach, and intestines (with contents), empty stomach, empty intestines, pancreas. A biphased curve with the first phase convex upward and the second phase convex downward represents the growth of eyeballs, hypophysis, suprarenals, and spleen. There are biphased curves, each phase represented by a straight line, for the epididymides; for the urinary bladder, the first phase is curved, the second straight. Irregular (triphased) curves are found to represent the growth of the testes and ovaries.

6. Individual variations are relatively great (especially in the later stages) in the weights of the stomach, intestines, spleen, thyroid gland, hypophysis, and suprarenal gland. The brain also shows an unusual degree of variability in weight.

7. In comparing the average weights of organs found in this series with the averages obtained by other observers, considerable discrepancy is found in some cases. This may be due to a number of variable factors aside from accidental individual variation, such as autopsy technique, dietary regime and environmental conditions in general, as well as possible inherent differences due to the race or variety of guinea-pigs used.

BIBLIOGRAPHY

JOSEPH, D. R. 1908 The ratio between heart-weight and the body-weight in various animals. Jour. Exper. Med., vol. 10, pp. 521–528.

LANTZ, D. E. 1918 Raising guinea-pigs. U. S. Dept. of Agr. Farmers' Bulletin 525.

LAZAREFF, N. 1895 (On the study of the change of weight and cellular elements of several organs and tissues in various periods of complete starvation.) Dissertation, Warsaw. (Russian.)

McCARRISON, R. 1921 Studies in deficiency disease. Oxford Med. Publ. London (see table X, p. 85).

MINOT, CHARLES S. 1891 Senescence and rejuvenation. Jour. of Physiol. vol. 12, pp. 97–153.

MÜHLMANN, M. 1899 Russische Literatur über die Pathologie des Hungerns (der Inanition). Zusammenfassendes Refarat, Centralbl. f. allg. Path., Bd. 10, S. 160–220; 240–242.

PAYTON, D. N. 1905 Relationship of thymus to the sexual organs. Jour. Physiol., vol. 32, pp. 28–32.

1911 Thymus and sexual organs. Jour. Physiol., vol. 42, pp. 267–282.

PAYTON, D. N., AND GOODALL, A. 1904 Contribution to the physiology of the thymus. Jour. Physiol., vol. 31, pp. 49–64.

READ, J. M. 1912 Observations on the suckling period in the guinea-pig. University of California, Publ. in Zoology, vol. 9, no. 7, pp. 341–351.

1913 The intrauterine growth-cycles of the guinea-pig. Arch. f. Entwicklungsmech. d. Org., Bd. 35, S. 708–723.

RICHET, CH. 1898 Article 'Cobaye.' Dictionnaire de Physiologie, vol. 3, pp. 863–948.

Reprinted from The American Journal of Physiology
Vol. 63, No. 2, January, 1923

CHANGES IN ORGAN WEIGHTS OF THE GUINEA PIG DURING EXPERIMENTAL SCURVY

D. H. BESSESEN

From the Department of Anatomy, University of Minnesota, Minneapolis

Received for publication October 17, 1922

McCarrison and others have observed a remarkable enlargement of the suprarenal glands in the guinea pig during experimental scurvy. The object of the present investigation is to study more carefully the extent of this enlargement in the various stages of scurvy, and to ascertain whether there are also changes in the weights of the other viscera. The work was done under the direction of Prof. C. M. Jackson, to whom I am indebted for advice and assistance.

For the animals used in this investigation, I am also obliged to Prof. R. Adams Dutcher, formerly in the Department of Agricultural Biochemistry of the University of Minnesota, who fed the guinea pigs in his laboratory. The scorbutic diet used was oats and water alone for the first fifteen animals; autoclaved milk was added to the diet for the remaining eleven. The curative diet was orange juice and green feed, with one exception in which boiled rhubarb juice was substituted for the orange juice. After the cure was apparently well established, the green feed alone was used. The twenty-six guinea pigs used are grouped as follows (see table 1):

Group I. Three animals, fed scorbutic diet for 5 days, and found apparently normal at autopsy.

Group II. Three animals, fed scorbutic diet for 10 days; appeared normal at autopsy, excepting a slight intestinal hyperemia.

Group III. Three animals, fed scorbutic diet for 15 days; appeared normal at autopsy, excepting slight intestinal hyperemia and slight congestion of the lungs.

Group IV. Two animals were fed scorbutic diet for 19 days. The autopsies showed a mild degree of scurvy. There were swellings of the costochondral junctions, ecchymoses into the muscles of the pectoral girdle, swelling and hemorrhage around the knee joint.

Group V. Eight animals were fed on scorbutic diet and died in 21

TABLE 1

Body weights of guinea pigs used

PIG NUMBER	SEX	MAXIMUM BODY WEIGHT IN GRAMS	FINAL BODY WEIGHT IN GRAMS	DIFFERENCE IN GRAMS	DIFFERENCE IN PER CENT	AVERAGE PER CENT DIFFERENCE FOR GROUP
Group I. 5 days on scurvy diet						
71	M	193	180.9	−12.1	−6.30	−5.8
70	M	244	227.5	−16.5	−6.78	
72	M	250	239.0	−11.0	−4.40	
Group II. 10 days on scurvy diet						
73	M	198	197.5	−0.5	−0.25	−6.3
74	M	248	236.4	−11.6	−4.68	
75	M	252	237.0	−15.0	−5.95	
Group III. 15 days on scurvy diet						
77	M	235	221.0	−14.0	−5.96	−4.5
78	M	250	234.0	−16.0	−6.40	
76	M	255	252.0	−3.0	−1.18	
Group IV. 19 days on scurvy diet Definite symptoms of beginning scurvy						
86	M	205	176.9	−28.1	−13.7	−16.3
82	F	225	182.8	−42.2	−18.8	
Group V. 21–54 days on scurvy diet Death from severe scurvy						
84	M	176	117.4	−58.6	−33.3	−37.0
85	M	228	118.0	−110.0	−48.3	
143	M	283	144.5	−138.5	−48.9	
122	F	295	167.8	−127.2	−43.1	
121	M	314	205.0	−109.0	−34.7	
130	F	386	267.0	−119.0	−30.8	
148	M	377	288.0	−89.0	−23.6	
123	F	438	291.0	−147.0	−33.6	
Group VI. 19–22 days on scorbutic diet. Then on antiscorbutic diet until apparently cured						
80	F	214*	158.9	−55.1	−25.7	+68.2
81	M	217*	253.5	+36.5	+16.8	
43	M		517.7			
289	M	314*	555.8	+241.8	+77.0	
292	M	325*	621.3	+296.3	+99.2	
290	M	304*	684.5	+380.5	+125.0	
294	M	328*	712.5	+384.5	+117.0	

* Maximum during period of scurvy diet.

to 54 days with a very severe type of scurvy. There were swellings of the wrists, knees and costochrondral junctions, intramuscular hemorrhages around the shoulders, knees and ribs, and "white lines" at the knees and costochondral junctions. The teeth were loose, the suprarenal glands very large and reddish yellow, the lungs and intestines congested.

Group VI. Seven animals were fed scorbutic diet 19 to 22 days and were then cured on orange or rhubarb juice with green feed given 18 days to 4 months. Autopsy showed permanent deformity of the osseous structures in only a few cases. The organs otherwise appeared normal.

With only one exception, the animals which did not die from scurvy were chloroformed. The autopsy was performed immediately after death. The head was sectioned from the body at the occipito-vertebral junction and the body suspended to drain the blood, while the brain, hypophysis and eyeballs were dissected clean from the skull. The thyroid gland was then carefully dissected out. Then the thorax was opened, the thymus (not included in the present study) excised, and the heart detached, opened and emptied of blood. The lungs, liver, spleen, pancreas, stomach, intestines, kidneys, suprarenals, testes or ovaries, and bladder were removed with as little adherent connective tissue as possible. The spinal cord was obtained by removing the roof of the bony canal, opening the dura and severing the nerve roots as close to the cord as possible. The organs were all kept in a closed container on moist filter paper and weighed on a balance accurate to the tenth of a milligram. The weights of the organs in the test animals are compared with the weights of normal organs (with corresponding body weight) as taken from the normal curves established by Bessesen and Carlson ('22) which show the normal growth of various organs in the guinea pig. In the following three tables are given the individual data for the body weight (table 1) and the suprarenals (table 2), and the group averages for the other organs (table 3). While the number of test animals used is relatively small, it appears sufficient to justify at least tentative conclusions as to the effects upon the weights of the various organs.

On comparing the initial with the final body weights (table 1) it is evident that there has been a slight loss, averaging only 5 or 6 per cent, in the first three test groups (up to 15 days). The loss increases to 16.3 per cent in the slightly scorbutic group (at 19 days) and to 37.0 per cent in those dying from scurvy. In the cured group VI, the body weight averages 68.2 per cent above the maximum during the period of scorbutic diet.

Since a scorbutic diet results in malnutrition, usually involving a marked loss in body weight, the question has frequently been raised as to whether the effects of scurvy may not be due, at least in part, to general inanition (ordinary starvation). Evidence upon this question is available by comparing the changes in weight produced by the two conditions in the various organs. The results of Lazareff ('95), who studied the weight changes in various organs (brain, spinal cord, heart, lungs, liver, spleen, kidneys, pancreas, stomach, intestines, bladder and skin) of guinea pigs starved with loss in body weight of 10 per cent to 36 per cent, are especially valuable for comparison in this connection.

For the organ weights of the present series (table 2 and 3), it must be remembered that the percentage differences do not represent the actual changes in weight, but merely the relation of the final organ weight to the normal for the corresponding final body weight.

Suprarenal glands (table 2). In groups I, II and III, the suprarenals usually appear slightly above normal in weight, but not much more than would result if these organs remained constant while the body weight decreased slightly. Making allowance for individual variations, it would therefore appear that the suprarenals maintain their original weight during the first 15 days on scorbutic diet. In stage IV at 19 days (beginning scurvy) with a loss in body weight of 16.3 per cent, the suprarenal glands average 78.8 per cent above normal. In group V (severe scurvy) with average loss in body weight of 37 per cent the weight of the suprarenals averages 270 per cent above the normal organ weight for corresponding (final) body weight. This would indicate that the enlargement of the suprarenals begins at about the same time that the symptoms of scurvy appear, but it becomes much greater in the later stages (in accordance with the observations of McCarrison). As may be noted in group VI, in some cases the hypertrophy of the suprarenals persists for some time after the scurvy is apparently cured.

Jackson ('15, '15a) found a slight increase in the weight of the suprarenals in underfed young rats and little or no loss in adult rats during starvation. Enlargement of the suprarenals was noted by Rondoni and Montagnani ('15) and Rondoni ('19) in guinea pigs starved or on diets of oats or maize.

McCarrison ('21) summarizing his earlier investigations (Indian Journ. Med. Research, 1919) found that the suprarenal glands enlarge in consequence of all classes of deficient dietaries, including total inanition as well as various vitamin deficiencies. In five guinea pigs fed on scorbutic diet, the average body weight decreased from 528 to

364 grams, a loss of about 31 per cent. The average weight of the suprarenals at autopsy was 0.955 gram, or practically double that in four normal controls (0.467 gram) of 627 grams average body weight.

TABLE 2

Suprarenal glands

STAGE OF EXPERIMENT	BODY WEIGHT IN GRAMS	WEIGHT OF SUPRARENALS IN GRAMS	NORMAL FOR CORRESPONDING BODY WEIGHT IN GRAMS	DIFFERENCE IN GRAMS	DIFFERENCE PER CENT	AVERAGE PER CENT DIFFERENCE FOR GROUP
5 days diet	180.9	0.1032	0.086	+0.0172	+20.0	+8.1
	227.5	0.0956	0.110	−0.0144	−13.1	
	239.0	0.1338	0.114	+0.0198	+17.4	
10 days diet	197.5	0.0858	0.095	−0.0092	−9.7	−7.4
	236.4	0.1317	0.113	+0.0187	+16.6	
	237.0	0.0916	0.113	−0.0214	−19.0	
15 days diet	221.0	0.1182	0.107	+0.0112	+10.5	+9.0
	234.0	0.1148	0.112	+0.0028	+2.5	
	252.0	0.1008	0.117	−0.0162	+13.9	
Beginning scurvy (19 days)	176.9	0.1502	0.083	+0.0672	+81.0	+78.8
	182.8	0.1553	0.088	+0.0673	+76.5	
Scurvy with death (21 to 54 days)	117.4	0.1798	0.050	+0.1299	+260.0	+270.1
	118.0	0.2733	0.052	+0.2213	+426.0	
	144.5	0.3049	0.065	+0.2399	+369.0	
	167.8	0.4049	0.078	+0.3269	+419.0	
	205.0	0.2871	0.099	+0.1881	+190.0	
	267.0	0.4230	0.122	+0.3010	+247.0	
	288.0	0.2890	0.130	+0.1590	+123.0	
	291.0	0.2977	0.131	+0.1667	+127.0	
Scurvy with cure	158.9	0.1480	0.074	+0.0740	+100.0	+29.3
	253.5	0.1916	0.118	+0.0736	+62.4	
	517.7	0.4645	0.227	+0.2375	+105.0	
	555.8	0.2205	0.258	−0.0375	−14.6	
	621.3	0.2750	0.327	−0.0520	−15.9	
	684.5	0.3390	0.403	−0.0640	−15.9	
	712.5	0.3695	0.438	−0.0685	−15.6	

Per kilo of final body weight, the suprarenals increased from 0.745 gram in the controls to 2.633 grams in the test animals. This is a difference of about 253 per cent, which corresponds closely with my result of 270 per cent in severe scurvy among younger (smaller) guinea pigs with slightly greater average loss in body weight (37 per cent). Similarly marked enlargements of the suprarenals were found by McCarrison in pigeons during total inanition or polyneuritis (autoclaved rice diet), and in monkeys on variously deficient diets. The changes in all cases are ascribed to inanition, the vitamins being "but links in the chains of materials requisite for perfect nutrition."

Enlargement of the suprarenal glands in scorbutic guinea pigs has also been observed by Bassett-Smith ('20). La Mer and Campbell ('20) found an increase in weight of the suprarenals proportional to the time during which the scrobutic diet is fed, but no increase during starvation. Vincent and Hollenberg ('20), however, found during inanition the weight of the suprarenals doubled in pigeons and dogs, and an even greater hypertrophy in rats.

Brain (table 3). In the first three groups, the average brain weight of the scorbutic guinea pigs appears nearly stationary, making allowance for individual variations. In the fourth group (at 19 days), it averages 12.4 per cent above normal, which is slightly less than would be expected if it had remained stationary in weight while the body weight decreased 16.3 per cent. In the fifth group (dead from scurvy) the brain apparently averages only 10.4 per cent above normal, although the loss in body weight averages 37 per cent.

This would indicate an actual marked loss in the absolute weight of the brain, though proportionately less than in the body as a whole. This loss in brain weight during scurvy is apparently greater than in starvation as reported by Lazareff ('95). He found an apparent loss of only about 6 per cent in the brain weight of guinea pigs starved with average loss of about 36 per cent in body weight. Similarly in the rat and other animals there is little or no apparent loss in brain weight during starvation (Jackson, '15). Bessesen and Carlson find an unusual amount of variability in the normal brain weight of the guinea pig, however, which may possibly explain the marked apparent loss in the scorbutic series as due to individual variations.

Spinal cord (table 3). The weight of the spinal cord appears above normal, varying from 28 to 69.8 per cent in the various groups. In part, this is most probably because the technique involved in the dissection included more of the tissues (nerve roots, meninges, etc.) than did that of Bessesen and Carlson, who established the norms with which my scorbutic animals were compared. If we admit this explanation and deduct a corresponding amount (about 30 per cent) for each of the various groups, we find that the weight of the spinal cord has apparently remained at approximately its original absolute weight. An increase in relative weight of the spinal cord would still be expected in the last two groups, but that in the fourth group is still too high for the corresponding loss in body weight. As there are only two animals in this group, allowance must be made for possible individual variations.

TABLE 3

Average percentage differences of organ weights compared with the normal. Final body weights compared with the initial weight; organs compared with normal for corresponding final body weight

PARTS	5 DAY TEST	10 DAY TEST	15 DAY TEST	BEGINNING SCURVY (19 DAYS)	DEATH FROM SCURVY (21–54 DAYS)
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Body weight	−5.8	−3.6	−4.5	−16.3	−37.0
Suprarenals	+8.1	−7.4	+9.0	+78.8	+270.1
Brain	+2.8	+0.3	−0.4	+12.4	+10.4
Spinal cord	+30.6	+40.6	+28.0	+62.0	+69.8
Eyeballs	+8.9	+6.8	+7.0	+20.8	+27.5
Thyroid	+14.3	+17.5	+6.4	+68.8	+21.2
Heart	+2.5	+2.4	−0.6	+11.1	+8.6
Lungs	−9.8	−5.8	+12.7	+4.8	+60.3
Liver	−25.0	−24.7	−18.0	+9.7	−1.0
Spleen	−20.8	−38.6	−18.2	+56.3	+35.0
Stomach-intestines (filled)	−7.0	+41.3	+23.2	−1.3	+7.1
Stomach-intestines (empty)	−25.2	−19.9	−8.4	+3.9	+36.3
Stomach	−3.5	−15.3	−10.7	+20.7	+7.9
Pancreas	+14.3	−13.7	−1.0	+29.6	−1.2
Kidneys	+9.9	+22.0	+7.0	+38.0	+57.7
Testes	+41.7	+31.1	+35.6	+76.4	+4.8
Epididymides	+47.2	+42.2	+45.4	+71.4	+75.2
Ovaries				−7.6	−19.8
Bladder	+37.3	+12.6	+9.7	+29.7	+44.7
Hypophysis	+8.0	+9.2	+12.9	+12.8	+50.5
Integument	−11.3	−19.4	−16.8	−13.0	−1.8

No data appear in the literature as to the weight of the spinal cord during scurvy. Lazareff ('95) found in the guinea pig during starvation a very slight loss in the weight of the spinal cord, similar to that of the brain.

Eyeballs (table 3). The average weight of the eyeballs appears above normal in all groups. A comparison of the corresponding body weights indicates that the eyeballs have maintained very nearly their original absolute weight, the apparent condition above normal being accounted for by the loss in body weight. No data have been recorded in the literature concerning the weight of the eyeballs of the guinea pig, either during scurvy or starvation. In other species, however, the eyeballs, like the nervous system, suffer little or no loss in weight during starvation (Jackson '15).

Thyroid gland (table 3). The thyroid gland appears above normal weight in all groups, but on account of the normal variability and the difficulty in the technique of dissection it is doubtful whether the apparent increase is significant. The results, therefore, do not confirm McCarrison's conclusion that the thyroid gland in guinea pigs on scorbutic diet increases to double or triple the original normal weight. In other types of deficiency (including total inanition) McCarrison found a tendency to atrophy in the thyroid gland of the monkey and pigeon. Jackson ('15) found a greater loss during chronic inanition than during acute inanition in the adult albino rat.

Heart (table 3). The heart maintains nearly normal weight in all groups, indicating a loss in weight almost proportional to the loss in body weight. McCarrison observed a relative decrease in the weight of the heart in scorbutic guinea pigs. On the other hand, La Mer and Campbell ('20) found some evidence indicating a hypertrophy of the heart in guinea pigs on scorbutic diet, which would accord with the findings in human scurvy, according to Hess ('20). Lazareff ('95) found that during total inanition in the guinea pig the decrease in the weight of the heart is nearly proportional to that of the whole body. The same holds true for the rat, with water, according to Jackson ('15).

Lungs (table 3). The lungs in my scorbutic animals show an average weight not far from normal, excepting group V (severely scorbutic) with weight 60.3 per cent above normal. McCarrison found a slight increase in weight of the lung in scorbutic guinea pigs. According to Hess ('20), pneumonia is a very frequent terminal infection in human scurvy, and this might explain the increased weight in my group of guinea pigs dead from scurvy. Lazareff ('95) observed a slight loss in absolute weight (with corresponding increase in relative weight) in the lungs of guinea pigs subjected to various degrees of starvation.

Liver (table 3). The liver in the guinea pigs on scorbutic diet shows a peculiar change in weight. In the earlier stages it averages about 25 per cent below normal, but recovers nearly normal weight after symptoms of scurvy appear. This corresponds in general with the observations of Lazareff ('95) on guinea pigs subjected to various degrees of starvation, the liver at first suffering a loss in weight relatively greater than that of the whole body, but in later stages returning to its normal relative weight. La Mer and Campbell ('20) find the liver weight unaffected by scorbutic diet. McCarrison, however, finds a marked decrease in both absolute and relative weight of the liver in guinea pigs on scorbutic diet.

Spleen (table 3). The spleen is notably variable in weight, even during health. In the first three groups on scorbutic diet there is a distinctly subnormal weight of spleen, which becomes apparently markedly above normal after scorbutic symptoms appear. A part of this increased weight is doubtless due to the marked hyperemia of the spleen which is evident at autopsy. According to Hess ('20), in human scurvy the spleen is usually enlarged and congested. McCarrison, however, found a marked loss of both absolute and relative weight in the spleen of scorbutic guinea pigs, as well as in various forms of inanition in the monkey and pigeon. In the guinea pig during starvation Lazareff ('95) found that the loss in weight of the spleen is roughly proportional to that of the body as a whole. Jackson ('15) cites evidence showing that during inanition in the rat and other species the spleen in general loses heavily in weight.

Stomach and intestines (table 3). When weighed with contents, these organs show an increased weight shortly after the animal has been placed on scorbutic diet (at the 10 day period), which decreases to normal before symptoms of scurvy appear. On the other hand, the empty gastro-intestinal tract appears about 25 per cent subnormal in weight in the first group, increasing progressively so as to reach approximately normal weight in the fourth group (beginning scurvy) and becoming 36.3 per cent above normal in the fifth (severely scorbutic) group. The (empty) stomach alone shows a less marked initial decrease and also a slighter increase later. The increased weight of the alimentary canal in the later stages is doubtless due in part to the characteristic congestion observed at autopsy, and likewise noted by Hess ('20) and McCarrison ('21). In guinea pigs subjected to various degrees of starvation, Lazareff ('95) found that the stomach loses but little in absolute weight. The loss is greater in the weight of the intestines, but proportionately less than in the body as a whole. Jackson ('15) found during inanition in the adult albino rat a decrease in weight of stomach and intestines relatively greater than that in the body as a whole.

Pancreas (table 3). The data for the various groups appear variable and inconclusive as to any marked change in the weight of the pancreas of scorbutic guinea pigs. Lazareff ('95) found the decrease during starvation proportional in general to that of the body. McCarrison finds a marked atrophy of the pancreas in pigeons and monkeys fed variously deficient diets.

Kidneys (table 3). All groups of my series show the kidney weight above normal. The increase is slight in the earlier stages, but very marked after scorbutic symptoms appear, and extreme (+ 57.7 per cent) in the severely scorbutic group. La Mer and Campbell ('20) likewise found the kidney weight increased in scurvy, which would agree with the condition of congestion found in the human kidney during scurvy, according to Hess ('20). McCarrison, on the other hand, observed a slight decrease in both relative and absolute weight of the kidneys in guinea pigs on scorbutic diet, as well as in other species on deficient diets. Jackson ('15) found during inanition in the adult albino rat a decrease in kidney weight proportional to the body weight.

Ovaries (table 3). The observations indicate an atrophy of the ovaries during scurvy, but the data are too few to warrant a definite conclusion.

Testes (table 3). The testes appear markedly above normal in all excepting the fifth (markedly scorbutic) group. This condition is surprising and difficult to interpret. In the fifth group it appears nearly normal, as likewise in the cured group (not included in the table). Jackson ('15) noted during inanition in rats a decrease in the testis weight proportional to body weight. McCarrison ('21) likewise observed atrophy of the testis in deficiently fed pigeons and monkeys.

Epididymides (table 3). The epididymides in the various test groups show the same enlargement as the testes, excepting the severe scurvy group, which for the epididymides shows an average weight of 75.2 per cent above the normal organ weight for the corresponding body weight. No data upon the weight of the epididymis in scurvy are available in the literature for comparison.

Hypophysis (table 3). The hypophysis weight averages above normal in all the groups, but none except the last group appears significant. In severe scurvy, however, it averages 50.5 per cent above normal for corresponding body weight. Since there is a loss of 37 per cent in body weight in this group, it is evident that in absolute weight the hypophysis has probably remained nearly unchanged in this as in the other groups. During inanition in the rat, Jackson ('15) found in starved rats a decrease in the weight of the hypophysis nearly proportional to that of the body. McCarrison, however, found but slight atrophy, and in some cases a hypertrophy on deficient diets.

Bladder (table 3). The urinary bladder appears above normal in all the groups. The high figure (+37.3 per cent) for the first group is probably due to accidental variation and therefore without significance. Otherwise the results do not differ greatly from what might be expected if the bladder were to remain nearly constant in absolute weight, while the body weight decreased in the various groups. McCarrison gives no weights for the bladder in scorbutic guinea pigs, but observed a marked congestion. This might tend to counteract a loss in weight from inanition-atrophy. The data of Lazareff ('95) indicate during total inanition in the guinea pig a loss in the weight of the bladder, but proportionately somewhat less than in the body as a whole.

Integument (table 3). In all the groups of my test animals, the skin is below normal, especially in the first four groups. This would indicate that the loss in weight of the integument is somewhat greater proportionately than in the body as a whole, although for the last (severely scorbutic) group the difference is insignificant. Allowance must be made for unavoidable differences in the technique of removal of the skin, as well as for individual variations. The data of Lazareff ('95) indicate that the loss of weight in the skin of the guinea pig during starvation is proportionately less than in the body as a whole. In the adult albino rat, Jackson ('15) found the loss nearly proportional to that of the body, the relative weight therefore remaining unchanged.

DISCUSSION AND SUMMARY OF RESULTS

The effects of a scorbutic diet upon the weights of the various organs of the guinea pig evidently vary greatly in the different viscera and also according to the length of the experiment. In most cases, during the first 15 days, the changes in weight are comparatively slight and probably of no significance. The spinal cord, testes, epididymides and urinary bladder appear markedly above normal in weight during this early period, however, while the liver, spleen, stomach-intestines and integument are definitely subnormal.

In the later stages, after the symptoms of scurvy are apparent, the changes in organ weight (as well as in body weight) are more evident. In comparison with the normal for corresponding (final) body weight, the ovaries alone appear definitely subnormal. The pancreas (late stage), heart, liver, testes (late stage) and integument appear nearly normal, indicating a loss in weight roughly proportional to that of the entire body. The brain, eye-balls, thyroid gland, spleen and intestines appear somewhat above normal, indicating some loss in absolute weight, but in most cases proportionately less than that of the entire body. The spinal cord, lungs (late stage) kidneys, epididymides, hypophysis (late stage) and urinary bladder are markedly above normal, indicating little or no loss in absolute weight, in spite of the great loss in body weight. The suprarenal glands have undergone a tremendous increase in absolute as well as in relative weight, so as to average 78.8 per cent above normal for corresponding body weight in the beginning scurvy group (with loss of 16.3 per cent in body weight) and 270.1 per cent above normal in those dead from scurvy (with 37 per cent loss in body weight.) The organs markedly above normal weight are usually congested, which may at least partly account for their increased weight. These results in general confirm and extend (to other organs) the observations of McCarrison and others, the differences being explainable partly on account of accidental variations, and partly as due to differences in technique, age of animals used, etc. More precision has been possible in the present work on account of having the norms of Bessesen and Carlson available for comparison.

The results also show a general agreement with those produced by starvation, somewhat tending to confirm McCarrison's view that the changes during scurvy (and other dietary deficiencies) are explainable as due to general inanition. The results in the two conditions are by no means identical, however, and marked differences in some of the organs (brain, lungs, spleen, kidneys, testes, epididymides and bladder) indicate that the scorbutic condition involves factors producing changes in weight different from those in ordinary inanition.

BIBLIOGRAPHY

Bassett-Smith. '20. Proc. Roy. Soc. Med. London, July, no. 9 (War Section), xiii, 51.
Bessesen, A. N., Jr. and H. A. Carlson. '22. Postnatal growth in weight of the body and of the various organs in the guinea pig (unpublished).
Hess, A. F. '20. Scurvy, past and present. Philadelphia and London.
Jackson, C. M. '15. Amer. Journ. Anat., xviii, 75.
'15 a. Journ. Exper. Zoöl., xix, 99.
La Mer, V. K. and H. L. Campbell. '20. Proc. Soc. Exper. Biol. and Med., xviii, 32.
Lazareff (Lasarew), N. '95. Dissert, Warsaw.
McCarrison, R. '21. Studies in deficiency disease. London. Also '19, Indian Journ. Med. Research, vi, 275, 550; vii, 188, 308.
Rondoni, P. '19. Brit. Med. Journ., May 3, 542.
Rondoni, P. and M. Montagnani. '15. Lo sper., lxix, 659.
Vincent, S. and M. S. Hollenberg. '20. Endocrinol., iv, 408.

203

MORPHOMETRY OF THE HUMAN FETUS WITH SPECIAL REFERENCE TO THE OBSTETRIC MEASUREMENTS OF THE HEAD

By

L. A. CALKINS, M.D., M.S., Ph.D.,
Minneapolis, Minn.

From the Department of Obstetrics and Gynecology and the Department of Anatomy of the University of Minnesota

Reprint from
THE AMERICAN JOURNAL OF
OBSTETRICS AND GYNECOLOGY
St. Louis

Vol. IV, No. 2, August, 1922

MORPHOMETRY OF THE HUMAN FETUS WITH SPECIAL REFERENCE TO THE OBSTETRIC MEASUREMENTS OF THE HEAD*

By L. A. Calkins, M.D., M.S., Ph.D., Minneapolis, Minn.

From the Department of Obstetrics and Gynecology and the Department of Anatomy of the University of Minnesota.

IT IS a well-recognized fact that present methods of determining the size and body proportions of the fetus *in utero* are distinctly inadequate. Estimation of age from the menstrual history is often as much as four weeks in error, while palpation of the abdomen is hardly more certain. The Mueller maneuver gives valuable information only in certain cases. Roentgenological estimation of the size of the fetal head has been entirely unsuccessful. In short, questions of disproportion between passage and passenger must remain, at present, unanswered while the problems of viability and maturity can be only partially solved. It is the aim of the present research to supply this much-needed information; and it is the purpose of this paper to present, in particular, that part of a study of fetal growth which deals with the obstetric measurements of the head.

In order to compare this series of measurements with other studies of the growth of the fetal head a brief review of the literature on this field is given here. Such related subjects as the measurements of

---

*Thesis presented to the Graduate School of the University of Minnesota, June, 1921, as a requirement for the Ph.D. (in Obstetrics and Gynecology). Read before American Association of Anatomists at Philadelphia, Mar. 24-26, 1921. Received for publication, Jan. 10, 1922.

The writer wishes to acknowledge his appreciation to Dr. J. C. Litzenberg for his helpful guidance, to Dr. F. L. Adair for his valuable aid in furnishing material and many important suggestions, to Dr. R. E. Scammon for his specific advice, and to all for their continued interest in this work.

Note: The Editor accepts no responsibility for the views and statements of authors as published in their ''Original Communications.''

the newborn, growth of other parts of the body, and of the body as a whole, will not be included in this discussion.

To Dr. J. Clarke[9] goes the credit of having made the first accurate study of either fetal or newborn heads. He attempted to determine why more stillbirths occurred in male than in female children. His procedure consisted in taking weights, horizontal head circumferences, and an ear to ear measurement over the vertex in 120 newborn children, 60 of each sex. He concluded that the larger head of the male accounted for the higher mortality in that sex.

Since that time many studies of the fetal head have been made, using as a basis for the analysis either body weight, or length of gestation, or both. Of these the more important are Spondli,[49] Pfannkuch,[41] Fehling,[12] Jousset,[26] Arnovljevic,[1] Brandt,[5] Bouillet,[4] Schaeffer,[45] LaTorre,[32] Dardel,[10] Faucon,[11] Weisz,[62] Corrado,[9a] Ballantyne,[2] Legou,[34] Retzius,[42] Friedenthal,[14] Michaelis,[39] Jackson,[24] Lutz,[36] Heuser,[20] Kjölseth,[28] Beneke,[3] and more recently and particularly Streeter.[51]

Pfannkuch[41] noted that the biparietal diameter was always 26.7 to 26.8 per cent of the sum of the biparietal, occipitofrontal and occipitomental diameters of the newborn head. In his own words he states: "Man auf diese Weise eine einfache Formel finden könnte, welche die eine grössere Annäherung an den Terminus *a quo* der Reife gestattet, als die einseitige Verwerthung eines Maasses es ermöglicht."

Probably the two most intensive attempts along this line so far are those of Kjölseth[28] and Corrado.[9a] Unfortunately Kjölseth did not publish her individual measurements and hence her work is not as valuable for the present study as that of Corrado who presented all of his individual readings. Kjölseth made observations upon 250 children born in the Kristiania Klinik. She chose the fourth day of postnatal life as the time to make her measurements. Her analysis was based upon sex of the child and age and parity of the mother; and she, like all other observers recording series of measurements in the literature, did not use body length as a basis for study. Corrado[9a] studied 250 dead fetuses. He used age and sex as a basis.

Jackson[24] has also made a study of head volume increase in fetal life.

Others who published individual head measurements include Spondli,[49] Spiegelberg,[48] Fehling,[12] Jousset,[26] Budin and Ribemont,[7] Faucon,[11] Weisz,[62] Legou,[34] Retzius,[42] Friedenthal,[14] Michaelis,[39] Heuser,[20] and Lutz.[36] These observations will be briefly described here.

Spondli,[49] studied 100 living newborn infants in Zurich.

Spiegelberg[48] measured 53 premature infants in Breslau in connection with a study of newborn measurements.

Jousset[26] published examples of the values of the different diameters for each month of pregnancy. It is not evident that more than one specimen for each month was so studied.

Budin and Ribemont[7] made observations on 39 dead, apparently fresh fetuses, in Paris.

Weisz[62] does not state the number of cases studied. His observations, as well as those of Lutz and Fehling, were based on living newborn fetuses of the last trimester of pregnancy. Lutz[35] measured height, weight, and horizontal head circumference on over 1000 cases in Berlin. Fehling[12] studied horizontal head circumference in 300 newborn infants in Leipzig.

Legou,[34] in Paris, made observations on 106 fetuses of the third to the sixth month.

Retzius[42] studied 48 and Friedenthal[14] 10 preserved specimens. Formalin was employed as preservative in most of Retzius' and in all of Friedenthal's specimens.

Michaelis[39] measured 100 dead, apparently fresh, fetuses.

Heuser[20] in Marburg made a graphic analysis, based on age, of 61 fetuses measured. His graphs are very striking but a close examination of his data indicates such definite results are not justified. By his own statement, he had too few cases from which to draw any definite conclusions.

Calderini[8] made a very extensive study of the bi-parietal and bitemporal diameters of the fetal head in the last three months of pregnancy. They are, however, published in such a form as to make them impossible of analysis.

Schaeffer[45] published only ranges for the values of the different dimensions in the different months of pregnancy. Neither individual measurements nor definite averages appear in this paper. This makes its value doubtful for the present analysis.

Several attempts to correlate the size and body proportions of the offspring with one, or the other, parent have also appeared in the literature; von Skalowski,[61] Gönner,[15] Heckmann,[18] Weisz,[62] and Riggs.[43] These are very interesting but not convincing. Moreover they deal with the newborn and older infants and do not properly come within the scope of this paper.

Hecker and Jellinghaus[25] found that the fetal head varied considerably in shape, and might, therefore, be very influential in determining the type of presentation. Sergi,[47] Tovo,[56] and Frassetto[13] described changes in the shape of the dried fetal skull at different periods of pregnancy, likening these different shapes to mathematical figures, as ellipsoidal, pentagonal, etc.

Ballantyne[2] was able to collect measurements of three apparently unmoulded heads and deduced therefrom average measurements for full term fetal heads *in utero.* He also made a study of the effects of birth molding on the different diameters of the head. Other students of the effects of labor on the shape of the fetal head include Swayne,[53] Runge,[44] Stumpf,[52] Mueller,[40] and Kaznelson.[27] Of these, Stumpf has brought out the most comprehensive piece of work, a study of birth molding in 66 cases. He took several measurements of the head at birth and repeated them several days later when the effects of molding had passed off, and yet before any considerable growth had occurred. This work is important, in determining the final condition *in utero,* but needs to be verified by a study of unmoulded heads.

MATERIAL AND METHODS

The material used consisted of some four hundred and fifty preserved human fetuses, from the collections of the Department of Anatomy and the Department of Obstetrics and Gynecology of the School of Medicine of the University of Minnesota. These were first carefully surveyed with the view to making use of only those heads which were not obviously abnormal, either in contour, or in size. It was found that some few specimens had been flattened posteriorly or laterally during preservation, either from too crowded quarters or from some other, less apparent, cause. Moreover, three were obviously hydrocephalic and one microcephalic. Another was acromegalic and another a negro. A few were found to be very soft and, hence, not desirable subjects for anthropometric study. All such undesirable specimens were eliminated, leaving only class A and a few of the class B of Streeter.[51] The selected group numbered three hundred and sixty-nine (369) specimens, ranging from 23 mm. to 544 mm. standing height. It was found that attempts to measure the different diameters and circumferences of specimens below 23 mm. standing height were attended with such a degree of uncertainty as to make the findings of little value. No specimens above 550 mm. standing height were used because of a grave doubt lest they might be distinctly postmature and that they would not represent the usual newborn characteristics. The series included six pairs of twins, and one set of triplets.

These specimens, arranged in groups of 5 cm. intervals, were distributed according to Table I.

All of the fetuses had been preserved in one of two ways. Those specimens which would be satisfactorily hardened in 10 per cent formalin were thus dealt with. A part of those over 30 to 35 centimeters standing height were first injected through the umbilical vein with a 10 per cent solution of formalin containing 1 per cent of chromic acid. The amount injected varied according to necessity in the judgment of the embalmer, Mr. M. Larson. Usually about 30 per cent of the body weight was used. These specimens were then kept in 10 per

TABLE I

DISTRIBUTION OF MATERIAL ACCORDING TO TOTAL LENGTH

Up to		49	mm.	standing	height	—17	specimens.
50	-	99	"	"	"	—29	"
100	-	149	"	"	"	—45	"
150	-	199	"	"	"	—28	"
200	-	249	"	"	"	—52	"
250	-	299	"	"	"	—46	"
300	-	349	"	"	"	—36	"
350	-	399	"	"	"	—36	"
400	-	449	"	"	"	—29	"
450	-	499	"	"	"	—24	"
500	-	549	"	"	"	—27	"

cent formalin. In order that variability in the effects of preservation might not alter the figures, no specimens were used which had been in the preservative less than six months. Many of them were two or more years in formalin solution.

The instruments used in making the measurements consisted of a steel meter tape, a brass bound wooden meter stick, and a sliding caliper, made of steel and accurately constructed. All of these were calibrated in millimeters and checked with one another very closely. The caliper carried a vernier scale, making possible readings to tenths of a millimeter where desirable. The arms of the caliper had sharp points on one side, flat bars on the other.

The linear measurements were usually taken with the calipers,—the exceptions will be spoken of later. The circumferences were taken with the steel tape except where the readings were 100 mm. or less. In these instances a heavy inelastic linen thread was wound around the part at the proper place, and the overlapping ends cut across with a sharp cataract scissors. The resulting circlet of thread was then measured with the caliper or tape. All readings were recorded in millimeters.

The measurements, taken on each specimen, were ten of the so-called obstetrical measurements of the head, along with the sitting and standing height. In a few of the specimens the lower jaw had previously been removed, thus prohibiting some of the measurements. In a few others some of the distances were not taken because of the presence of an unusually large caput succedanum or for some other, equally good, reason.

The measurements taken, and the technics employed for each, were as follows:

1. Sitting height, or crown-rump (C. R.), was taken with the body in an extended attitude (as one would sit erect) with the chin and thighs as nearly as possible at right angles with the body. The readings were taken with the sliding caliper except where the specimens were too long. For these a sliding caliper, in effect, was made from the meter stick, laid parallel to the body and perpendic-

TABLE II
OCCIPITO-FRONTAL-DIAMETER OF HEAD (GLABELLA-INION)
.235 C.H.(MM)+4.0MM.: (369 CASES)

Crown Heel Length (mm.)		Crown Rump Length (mm)	Occipito-Frontal Diameter (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max.	Min.	Mean (a)		mm.	Percent.		CH Length (cm)	Value (mm)	Percent increment
23-50	37.2	31.4	18	10	13.7	12.7	-1.0	-7.3	17	5	15.75	—
50-100	75.4	57.0	27	14	21.7	21.7	0.0	0.0	29	10	27.50	75
100-150	124.2	88.9	39	26	33.2	33.2	0.0	0.0	45	15	39.25	43
150-200	172.8	119.4	51	38	44.7	44.6	-0.1	-0.2	28	20	51.00	30
200-250	225.3	152.3	68	48	57.9	56.9	-1.0	-1.7	52	25	62.75	23
250-300	272.1	183.9	78	60	69.2	68.6	-0.6	-0.9	46	30	74.50	19
300-350	323.9	223.7	90	71	80.0	80.1	+0.1	+0.1	36	35	86.25	16
350-400	370.6	248.2	101	79	88.8	91.1	+2.3	+2.6	36	40	98.00	13
400-450	423.6	287.9	115	87	99.9	103.5	+3.6	+3.6	29	45	109.75	12
450-500	471.4	318.5	123	99	109.2	114.8	+5.6	+5.1	24	50	122.50	10
500-544	523.4	358.1	129	105	117.2	127.0	+9.8	+8.4	27	55	134.25	9

TABLE III
BI-PARIETAL DIAMETER OF HEAD (MAXIMUM)
.19 C H (MM) + 2.0 MM. (369 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm)	Bi-Parietal Diameter (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max	Min	Mean (a)		mm	Per cent		C H Length (cm)	Value (mm)	Per cent increment
23-50	37.2	31.4	12	6	9.5	9.1	-0.4	-4.2	17	5	11.5	—
50-100	75.4	57.0	20	10	16.2	16.3	+0.1	+0.6	29	10	21.0	83
100-150	124.2	88.9	32	21	26.3	25.6	-0.7	-2.7	45	15	30.5	45
150-200	172.8	119.4	41	29	35.5	34.8	-0.7	-2.0	28	20	40.0	31
200-250	225.3	152.3	54	35	45.3	44.8	-0.5	-1.1	52	25	49.5	24
250-300	273.1	183.9	66	43	53.9	53.9	0.0	0.0	46	30	59.0	19
300-350	323.9	223.7	77	52	62.5	63.5	+1.0	+1.6	36	35	68.5	16
350-400	370.6	248.2	78	58	69.6	72.4	+2.8	+4.0	36	40	78.0	14
400-450	423.2	287.9	84	66	77.3	82.4	+5.1	+6.6	29	45	87.5	12
450-500	471.4	318.5	99	70	87.0	91.6	+4.6	+5.3	24	50	97.0	11
500-544	523.4	358.1	102	85	94.0	101.4	+7.4	+7.9	27	55	106.5	10

ular bars applied to it at the proper places. No compression was exercised in taking the readings.

2. Standing height, or crown-heel (C. H.), was found by adding trochanter-to-heel, less trochanter-to-rump to the sitting height, in each case care being exercised to find the center of the trochanter. In those specimens in which it was found impossible to extend the legs on the thighs the trochanter-to-heel measurement was taken in two segments. Trochanter to the center of the lateral surface of the knee joint was first taken, and to this was added the distance from the latter point to the heel. These two measurements were taken uniformly along the right side of the body and were all checked at least once to insure the highest possible degree of accuracy.

3. Head length, or the occipito-frontal diameter (O. F.), was taken from glabella to inion, the longest diameter without respect to the horizontal.

4. Suboccipito-frontal diameter (S. O. F.) was taken from the obstetrical joint (the union of superior and lateral portions of the occipital bone) to the most distant point on the frontal bones.

TABLE IV

SUBOCCIPITO-BREGMATIC DIAMETER OF HEAD

.2 CH (MM) + 6.0MM (368 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm)	Suboccipito-Bregmatic Diameter (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max	Min	Mean (a)		mm.	Per cent		CH Length (cm)	Value (mm)	Per cent increment
23-50	37 2	31 4	17	9	13 2	13 4	+02	+1 5	17	5	160	—
50-100	75 4	57 0	25	12	21 0	21 1	+01	+0.5	29	10	260	63
100-150	124 2	88.9	40	24	31.4	30 8	-0.6	-1 9	45	15	360	38
150-200	172 8	119 4	48	37	41 6	40 6	-1 0	-2 4	28	20	460	28
200-250	225 3	152.3	63	43	52 5	51 1	-1 4	-2 7	52	25	56.0	22
250-300	273 5	184 1	70	51	61 8	60.7	-1 1	-1 8	45	30	660	18
300-350	323 9	223 7	82	62	71 0	70.8	-0.2	-0 3	36	35	760	15
350-400	370 6	248 2	88	67	79 9	80.1	+0 2	+0.3	36	40	860	13
400-450	423 2	287 9	96	78	87.9	90.6	+2.7	+3 1	29	45	960	12
450-500	471 4	318.5	109	83	95 2	100 3	+5.1	+5 4	24	50	106.0	10
500-544	523.4	358 1	110	94	102.3	110	+8 4	+8.2	27	55	116.0	9

TABLE V

SUBOCCIPITO-FRONTAL DIAMETER OF HEAD

215 CH (MM.) + 70MM (368 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm)	Suboccipito Frontal Diameter (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max	Min	Mean (a)		mm	Per cent		C H Length (cm)	Value (mm)	Per cent increment
23-50	37 2	31 4	18	10	14 5	14 9	+0 4	+2 8	17	5	17 75	—
50-100	75 4	57 0	28	15	22 4	23 2	+0 8	+3 6	29	10	28 5	61
100-150	124 2	88 9	41	25	33 6	33 7	+0 1	+0 3	45	15	39 25	38
150-200	172 8	119 4	50	38	44 8	44 2	-0 6	-1 3	28	20	50 00	27
200-250	225 3	152 3	65	47	56 9	55.4	-1 5	-2 6	52	25	60 75	22
250-300	273 2	184 1	77	58	67 1	65.8	-1 3	-1 9	45	30	71 50	18
300-350	323 9	223 7	87	68	76.3	76 6	+0 3	+0 4	36	35	82 25	15
350-400	370 6	248 2	97	73	85 1	86 7	+1 6	+1 9	36	40	93 00	13
400-450	423 2	287 9	108	82	93 6	98 0	+4 4	+4 7	29	45	103 75	12
450-500	471 4	318.5	115	89	102 4	108 4	+6 0	+5 9	24	50	114 50	10
500-544	523 4	358 1	118	99	111 0	119 5	+8 5	+7 7	27	55	125 25	9

5. Suboccipito-bregmatic diameter (S. O. B.) was found by taking a similar measurement whose second point was the median point of the coronal suture.

6. Occipito-mental diameter (O. M.) was measured from menton to inion.

7. Head width, or bi-parietal diameter (Bi.-P), was always the greatest width of the head above the external auditory meati. This was found, almost always, over the parietal eminences.

8. Horizontal head circumference (H. H. C.) was taken around glabella and inion.

9. Suboccipito-frontal circumference (S. O. F. C.) was taken around the points over which the corresponding diameter was measured.

10. Suboccipito-bregmatic circumference (S. O. B. C.) was also found in a similar manner to the corresponding diameter.

11. Occipital-mental circumference (O. M. C.) was taken around menton and inion.

12. A circumference, designated as "large circumference" (L. C.) was taken around menton and superior tip of occipital bone. This is not the largest cir-

cumference of the head, as Ballantyne[2] and others have shown. It was chosen in preference to the largest circumference because of more definite landmarks, and because of more frequent mention in obstetrics.

A very slight uniform pressure was used in all of the measurements with the idea of entirely avoiding compression, and yet not allowing

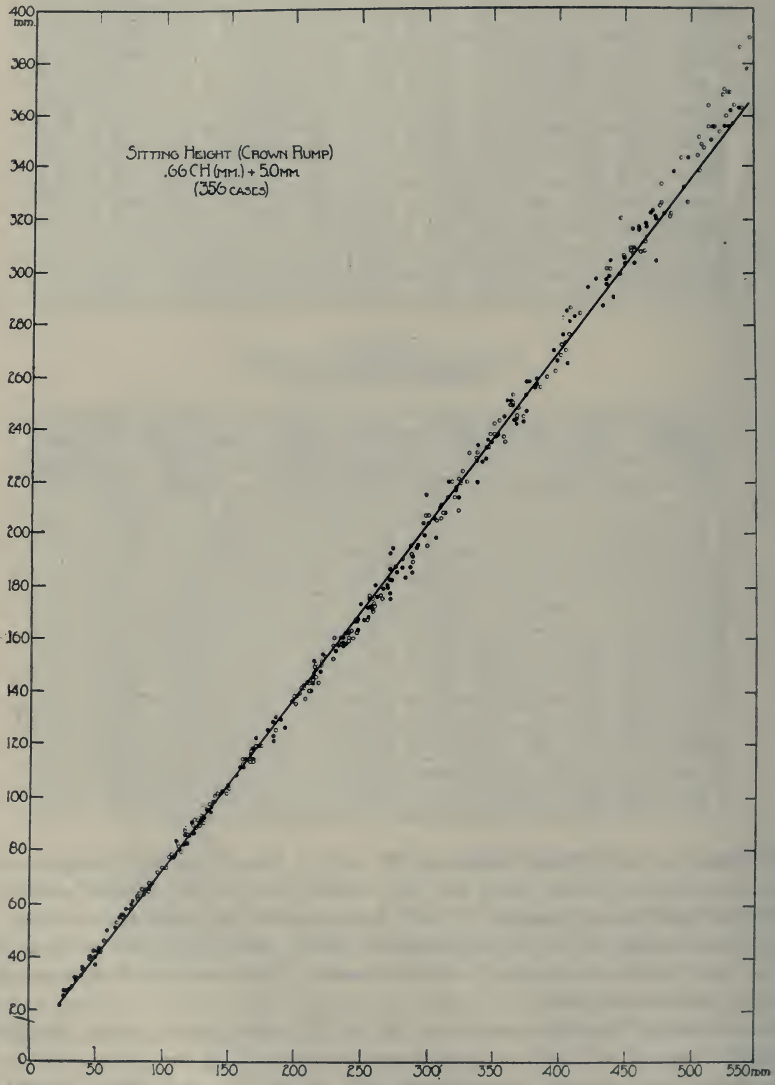


Fig. 1.

to allow the external moisture to evaporate, and yet not long enough to allow any "drying out." The length of time varied, according any slack to be present in the measuring tape. The specimens were also removed from the solutions, long enough previous to measuring, to size, from a few minutes for the smaller ones to nearly an hour for the larger ones. All measurements were recorded in millimeters, and will so appear in all succeeding tables and figures.

As soon as the series of readings was completed they were assembled and arranged in a table which on account of its length is not published but may be found on file in the Wistar Institute of Anatomy, of Philadelphia. The amount of variation in the individual measurements was, on the whole, very slight.

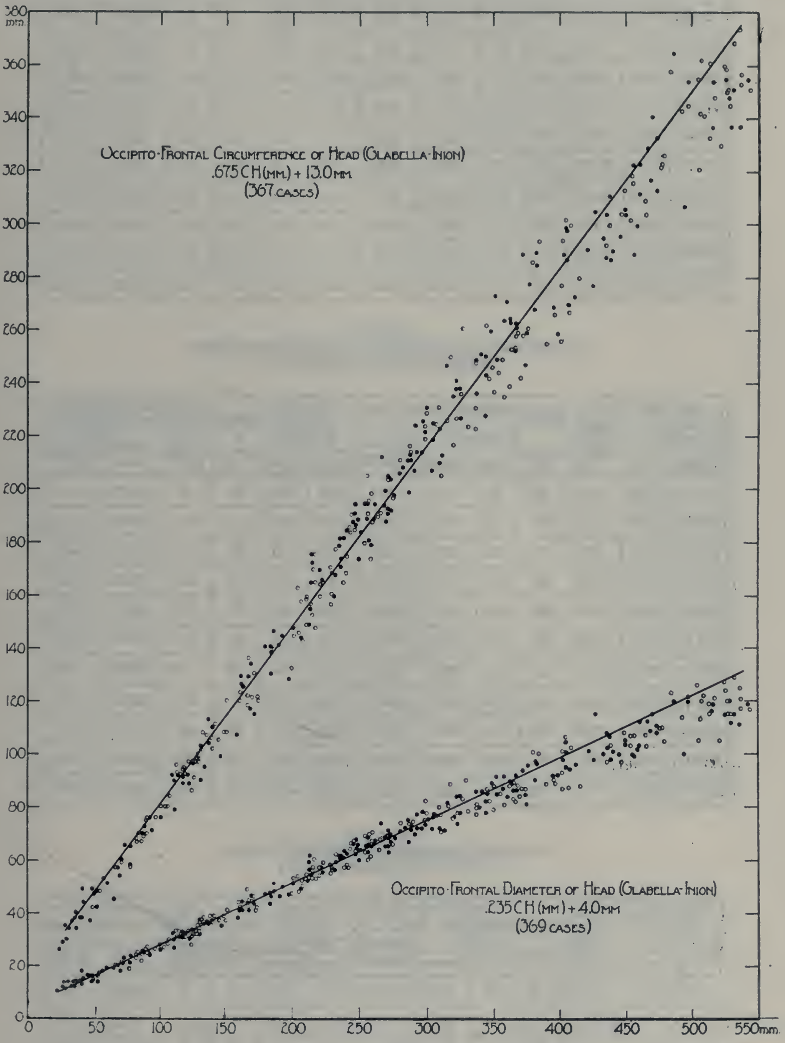


Fig. 2.

The crown rump (C.R.) was then plotted, as ordinate, on coordinate paper, against the crown heel (C.H.), as abscissa. The resulting field graph is shown in Fig. 1. The males are represented by dots, the females by circles. Where the specimens were so small as

TABLE VI
OCCIPITO-MENTAL DIAMETER OF HEAD (MENTON-INION)
.235 C.H. (MM) + 2.0 MM. (365 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm.)	Occipito-Mental Diameter (mm.)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm. Intervals of Crown Heel Length		
			Observed			Calculated						
Range	Mean		Max	Min.	Mean (a)	Mean (b)	mm.	Per cent		C.H. Length (cm)	Value (mm)	Per cent Increment
23-50	36.6	30.9	16	8	12.1	10.6	-1.5	-12.4	16	5	13.75	—
50-100	75.4	57.0	25	14	20.1	19.7	-0.4	-2.0	29	10	25.50	85
100-150	124.2	88.9	36	24	30.5	31.2	+0.7	+2.3	45	15	37.25	46
150-200	172.8	119.4	48	37	42.1	42.6	+0.5	+1.2	28	20	49.00	32
200-250	225.3	152.3	66	47	56.1	54.9	-1.2	-2.1	50	25	60.75	24
250-300	273.5	184.1	76	58	67.8	66.3	-1.5	-2.2	45	30	72.50	19
300-350	323.9	223.7	88	70	79.5	78.1	-1.4	-1.8	36	35	84.25	16
350-400	370.6	248.2	104	82	89.6	89.1	-0.5	-0.6	36	40	96.00	14
400-450	423.2	287.9	107	89	100.2	101.5	+1.3	+1.3	29	45	107.75	12
450-500	471.4	318.5	129	103	112.7	112.8	+0.1	+0.1	24	50	119.5	11
500-544	523.4	358.1	142	112	123.4	125.0	+1.6	+1.3	27	55	131.25	10

TABLE VII
OCCIPITO-FRONTAL CIRCUMFERENCE OF HEAD (GLABELLA-INION)
.675 C.H. (MM) + 13.0 MM. (367 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm.)	Horizontal Head Circumference (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm. Intervals of Crown Heel Length		
			Observed			Calculated						
Range	Mean		Max.	Min.	Mean (a)	Mean (b)	mm	Per cent		C.H. Length (cm)	Value (mm)	Per cent Increment
23-50	36.6	31.0	49	26	37.5	37.7	+0.2	+0.5	16	5	46.75	—
50-100	75.4	57.0	76	42	61.9	63.9	+2.0	+3.2	29	10	80.50	72
100-150	124.2	88.9	113	76	95.6	96.8	+1.2	+1.3	45	15	114.25	42
150-200	172.8	119.4	146	107	131.8	129.6	-2.2	-1.7	28	20	148.00	30
200-250	225.3	152.3	194	142	167.1	165.1	-2.0	-1.2	52	25	181.75	24
250-300	273.1	183.9	225	173	199.8	197.3	-2.5	-1.3	46	30	215.50	19
300-350	323.9	223.7	261	204	232.6	231.6	-1.0	-0.4	36	35	249.25	16
350-400	369.9	248.2	293	234	260.2	262.7	+2.5	+1.0	35	40	283.00	14
400-450	423.2	287.9	312	255	290.6	298.7	+8.1	+2.8	29	45	316.75	12
450-500	471.4	318.5	364	288	322.9	331.2	+8.3	+2.6	24	50	350.50	11
500-544	523.4	358.1	373	320	348.5	366.3	+17.8	+5.1	27	55	384.25	10

TABLE VIII
SUBOCCIPITO BREGMATIC CIRCUMFERENCE OF HEAD
.625 C.H. (MM) + 16.0 MM (365 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm)	Suboccipito Bregmatic Circumference (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated						
Range	Mean		Max	Min	Mean (a)	Mean (b)	mm	Per cent		C.H. Length (cm)	Value (mm)	Per cent increment
23-50	36.6	31.0	48	28	37.4	38.9	+1.5	+4.0	16	5	47.25	—
50-100	75.4	57.0	76	41	61.7	63.1	+1.4	+2.3	29	10	78.50	66
100-150	124.1	88.8	110	75	94.6	93.6	-1.0	-1.1	44	15	109.75	40
150-200	172.8	119.4	140	106	124.0	124.0	0.0	0.0	28	20	141.00	28
200-250	225.3	152.3	184	130	160.2	156.8	-3.4	-2.1	52	25	172.25	22
250-300	273.5	184.1	210	161	191.3	186.9	-4.4	-2.3	45	30	203.50	18
300-350	323.9	223.7	247	195	222.2	218.4	-3.8	-1.7	36	35	234.75	15
350-400	369.9	248.2	281	221	248.3	247.2	-1.1	-0.4	35	40	266.00	13
400-450	423.2	287.9	291	246	273.2	280.5	+7.3	+2.7	29	45	297.25	12
450-500	471.4	318.5	352	262	303.8	310.6	+6.8	+2.2	24	50	328.50	11
500-544	523.4	358.1	347	308	326.3	343.1	+16.8	+5.1	27	55	359.75	10

TABLE IX
SUBOCCIPITO-FRONTAL CIRCUMFERENCE OF HEAD
.65 C H (MM.) + 15.0 MM (366 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm)	Suboccipito Frontal Circumference (mm.)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max	Min	Mean (a)		mm.	Per cent		C H Length (cm)	Value (mm)	Per cent increment
23-50	36.6	31.0	50	28	39.0	38.8	-0.2	-0.5	16	5	47.5	—
50-100	75.4	57.0	78	45	62.9	64.0	+1.1	+1.7	29	10	80.0	68
100-150	124.2	88.9	115	75	96.8	95.7	-1.1	-1.1	45	15	112.5	41
150-200	172.8	119.4	143	111	132.7	127.3	-5.4	-4.1	28	20	145.0	29
200-250	225.3	152.3	192	141	166.5	161.4	-5.1	-3.1	52	25	177.5	22
250-300	273.5	184.1	224	170	197.7	192.8	-4.9	-2.5	45	30	210.0	18
300-350	323.9	223.7	257	201	227.8	225.5	-2.3	-1.0	36	35	242.5	15
350-400	369.9	248.2	284	225	254.5	255.4	+0.9	+0.4	35	40	275.0	13
400-450	423.2	287.9	300	248	280.3	290.1	+9.8	+3.5	29	45	307.5	12
450-500	471.4	318.5	354	280	312.3	321.4	+9.1	+2.9	24	50	340.0	11
500-544	523.4	358.1	367	319	338.9	355.2	+16.3	+4.8	27	55	372.5	10

TABLE X
OCCIPITO-MENTAL CIRCUMFERENCE OF HEAD (MENTON-INION)
.63 C.H. (MM.) + 9.0 MM (355 CASES)

Crown Heel Length (mm.)		Crown Rump Length (mm)	Occipito-Mental Circumference (mm.)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max	Min	Mean (a)		mm.	Per cent.		C H Length (cm)	Value (mm)	Per cent increment
23-50	35.9	30.5	47	23	33.4	31.6	-1.8	-5.4	15	5	40.5	—
50-100	75.4	57.0	73	40	53.6	56.5	+2.9	+5.4	29	10	72.0	78
100-150	123.5	88.4	101	63	83.5	86.8	+3.3	+4.0	43	15	103.5	44
150-200	172.8	119.4	135	95	117.5	117.9	+0.4	+0.3	28	20	135.0	30
200-250	225.3	152.3	181	125	156.0	150.9	-5.1	-3.3	50	25	166.5	23
250-300	273.1	183.9	217	162	186.6	181.1	-5.5	-2.9	46	30	198.0	19
300-350	323.9	223.7	257	190	219.8	213.1	-6.7	-3.0	36	35	229.5	16
350-400	369.9	248.2	279	213	245.9	242.0	-3.9	-1.6	35	40	261.0	14
400-450	423.5	288.1	297	230	270.9	275.8	+4.9	+1.8	28	45	292.5	12
450-500	471.5	318.3	367	269	308.4	306.0	-2.4	-0.8	23	50	324.0	11
500-544	523.3	358.4	380	307	336.2	339.9	+3.7	+1.1	22	55	355.5	9

TABLE XI
LARGE CIRCUMFERENCE OF HEAD (MENTON-LAMBDA)
.72 C H (MM) + 10.0 MM (343 CASES)

Crown Heel Length (mm)		Crown Rump Length (mm)	Large Circumference (mm)				Difference between (a) and (b)		Number of cases	Calculated Values at 5cm Intervals of Crown Heel Length		
			Observed			Calculated Mean (b)						
Range	Mean		Max	Min	Mean (a)		mm	Per cent		C H Length (cm)	Value (mm)	Per cent increment
23-50	35.9	30.5	46	27	36.7	35.8	-0.9	-2.5	15	5	46.0	—
50-100	75.4	57.0	78	44	62.0	64.3	+2.3	+3.7	29	10	82.0	78
100-150	123.5	88.4	112	79	96.8	98.9	+2.1	+2.2	42	15	118.0	44
150-200	173.2	119.6	153	116	134.6	134.7	+0.1	+0.1	27	20	154.0	31
200-250	225.3	152.3	199	149	174.7	172.2	-2.5	-1.4	50	25	190.0	23
250-300	271.7	182.1	233	182	207.4	205.6	-1.8	-0.9	43	30	226.0	19
300-350	323.9	223.7	282	214	246.1	243.2	-2.9	-1.2	36	35	262.0	16
350-400	369.3	248.6	300	253	276.2	276.0	-0.2	-0.1	33	40	298.0	14
400-450	421.8	286.3	335	278	310.9	313.7	+2.8	+0.9	23	45	334.0	12
450-500	474.0	321.0	402	330	355.3	351.3	-4.0	-1.1	20	50	370.0	11
500-544	523.3	359.2	407	358	383.9	386.8	+2.9	+0.8	25	55	406.0	10

to make the sex indeterminate the symbol ⊗ was used. The grouping of the several points was so close that similar graphs of the other measurements were made, Figs. 2 to 6. In each one, the diameter, or circumference, under consideration was plotted as ordinate, against the crown heel (C. H) as abscissa, and the same plan of distinguishing sex was employed.

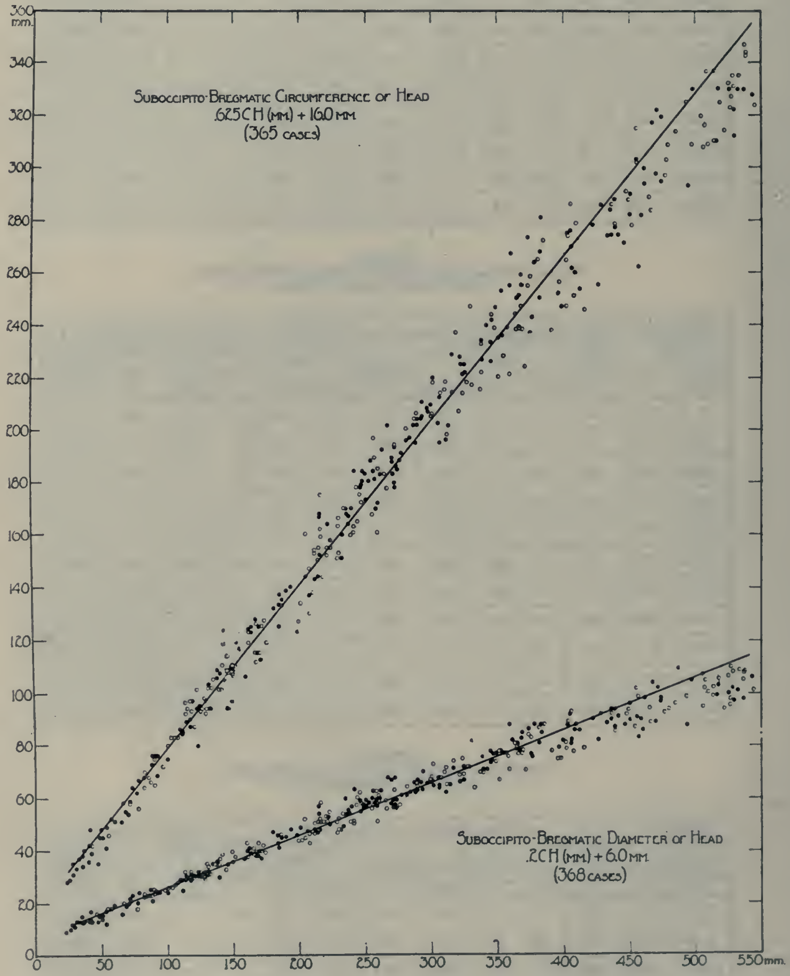


Fig. 3.

It was not at once evident which method of drawing the curves through these graphs would be the most satisfactory. Each of the three most common methods, not including inspection, namely, the weighted median, the weighted average, and the arithmetic average weighted by the median crown-heel height was tried, and equally satisfactory curves resulted. The method of the averages* was chosen as being the one more commonly used, and, perhaps, the more readily comprehensible.

Fig. 7 with its solid line represents the field graph and resultant curve for the formalin preserved material, and, as such may be taken as quite representative of any series of Caucasian fetuses, similarly preserved. Similar curves resulted for the other measurements studied.

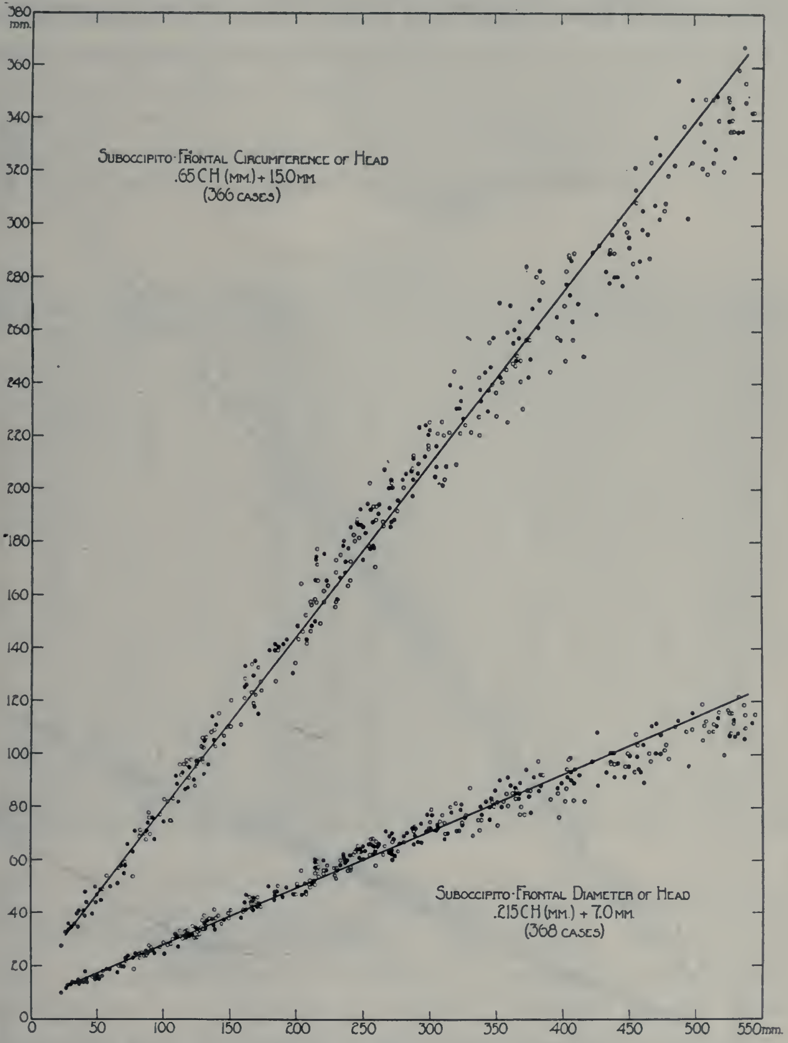


Fig. 4.

---

*The arithmetic average, for example, of the occipitofrontal diameters of the cases in each five centimeter interval was plotted against the arithmetic average of the crown heel lengths for the same cases. The curve was drawn through these resulting points.

The data for the plotting of these curves along with the range for the separate intervals, appears in columns 1 to 6 of Tables II to XI.

SUMMARY

These curves were quite striking in their characteristics. The curve for Fig. 5 and the upper graph in Fig. 6 were practically straight lines throughout. In Fig. 1 there resulted a straight line up to about 300 mm. standing height, at which point there was a deflection toward the vertical. The remaining curves were deflected downward at 300-350 mm. standing height from straight lines below that point. Feeling that these deflections might be artifacts, due to the type of

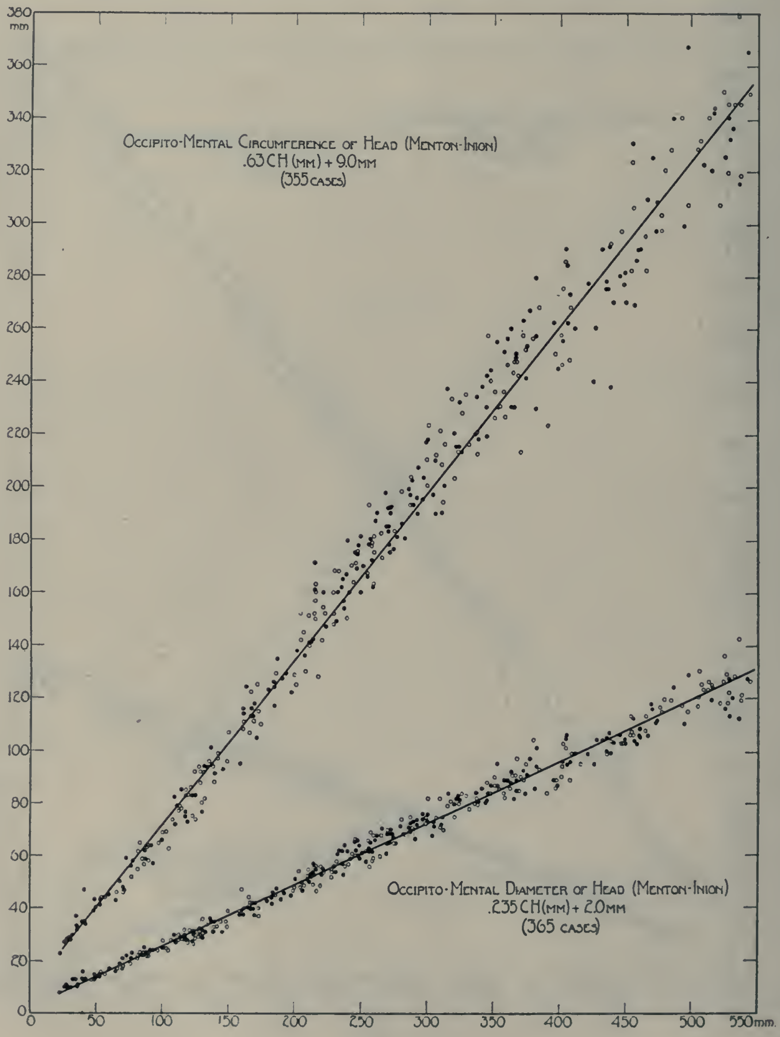


Fig. 5.

material, the writer undertook two other sets of investigations to determine:

1. The effects of preservation, as carried out on this material, and
2. The effects of birth moulding.

A chance observation of the injection process suggested the plan to be followed in the first of these two studies. Along with similar changes in the trunk, the cranial vault can be seen to increase in size, as one of these fetuses is injected through the umbilical vein. At the same time, and as a natural result of this swelling, the overriding of the cranial bones produced by birth moulding is, in part, eradicated. One might immediately arrive at the conclusion that such injected fetuses would, at least in some respects, better represent the fetus *in utero* than the uninjected newborn material. This eventually proved to be the case. The detailed plan of study adopted was as follows: (1) measure fresh specimen; (2) measure again immediately after injection. (3) measure at monthly intervals for six months, omitting the fifth, to determine the changes following immersion in formalin. For the smaller fetuses which were not primarily injected, items 1 and 3 were carried out in a similar manner. The results obtained in this latter study on the uninjected specimens were quite significant. For the various measurements the averages obtained are shown in Table XIII.

TABLE XII
MEASUREMENTS OF UNMOULDED HEADS (MM)
(LIVING INFANTS)

Period of Development	Name	Sex	Age in Hours	Parity of Mother	Method of Delivery	Crown Heel Length	Head Diameters					Head Circumferences					Palpable Moulding
							OF	BIP	SOB	SOF	OM	HHC	SOBC	SOFC	OMC	LC	
Premature	Be	M	29	?	S.	394	101	79	88	95	96	290	271	277	257	307	None
	716	M		?	Post.	396	96	77	88	89	95	272	258	262	248	289	- (Dead)
	Wl	M	28½	I	C.S.	470	111	90	100	103	105	326	305	310	283	330	-
	Br	F	1	VII	S	475	116	88	96	106	115	324	295	315	295	335	Very slight
	We	F	2	I	S.	475	112	87	97	102	106	320	297	307	277	330	Slight, transverse
Mature	Pa	F	4	I	S.	480	118	89	95	103	115	338	305	312	310	345	None
	Es	M	6½	IV	C.S.	485	126	103	109	118	117	360	339	349	335	387	-
	McA	M	1½	?	S.	490	124	93	104	113	120	355	320	331	310	360	Slight, ant-post
	Fl	F	25½	I	S.	490	122	91	99	110	111	338	307	319	291	355	Slight
	Ca	F	1½	V	S.	490	117	95	102	112	115	334	320	326	310	350	None
	Mo	M	3½	I	S.	490	124	93	105	114	121	351	324	331	280	360	Slight
	Br	M	7	II	C.S.	495	119	94	104	112	124	334	308	327	306	360	None
	Wo	M	3	I	S.	498	122	101	100	112	118	355	330	335	310	358	Slight, ant-post
	Bra	M	½	I	S.	500	123	102	97	111	125	365	325	346	333	385	Little ant-post
	Sa	F	2	I	S.	500	117	102	107	111	120	347	318	342	322	367	None
	O'N	M	7½	V	S.	500	124	93	106	116	119	345	330	334	325	360	
	Ga	M	19½	I	S.	500	118	97	103	109	115	342	319	325	318	358	Slight, ant-post
	Gr	F	5	?	S.	500	123	101	108	110	125	353	322	328	312	382	None
	Sw	M	10	?	S.	505	114	97	104	112	114	343	326	328	312	354	Slight ant-post
	O'C	M	1	II	S.	505	129	97	108	116	116	358	332	340	310	365	None
	Su	F	6½	?	S.	506	125	98	108	122	127	363	339	355	346	377	
	Al	M	6½	IV	S.(t)	510	121	92	105	115	113	347	327	335	302	342	Slight transverse
	As	M	1½	II	S.	510	123	101	102	111	125	358	330	338	335	379	- ant-post
	Cl	F	13	I	S.(t)	510	125	95	102	114	121	347	317	335	310	355	None
	Ba	M	23	?	S.(t)	515	128	100	114	120	120	366	342	351	320	375	•
	Fe	F	¼	VI	S.	515	121	98	103	114	120	352	327	340	310	362	
	Go	M	6½	III	C.S.	520	120	101	104	113	124	357	347	354	305	380	-
	Il	M	4	VI	S.	520	117	102	108	113	115	354	340	348	327	383	Slight, ant-post
	En	M	2	I	S.	520	115	91	106	110	116	330	318	325	312	350	None
	Wo	M	21½	V	S.	525	116	94	100	112	117	339	323	334	317	357	
	Kl	M	3½	I	S	528	132	104	110	115	123	375	345	348	332	384	Slight, ant-post
	Ora	F	14	I	S.	535	137	106	119	127	126	385	367	373	320	400	
Average Newborn			8⅙			505	122	97	105	114	119	352	328	337	316	366	
Postmature	Ra	M	7½	I	S	570	124	103	109	117	125	365	341	355	322	385	Moderate, ant-post

Preservation by the immersion in formalin alone effects but little change in the dimensions under consideration. The changes noted are each well within the limit of error in measuring those diameters and can therefore be neglected as far as correcting the curves in Figs. 1 to 6 is concerned. This is particularly true since the size of specimen seemed to bear no relation to the percentage change which occurred in that specimen. Only ten fetuses were so studied; but, in view of the almost negative results, such a number of cases is probably sufficient for all practical purposes.

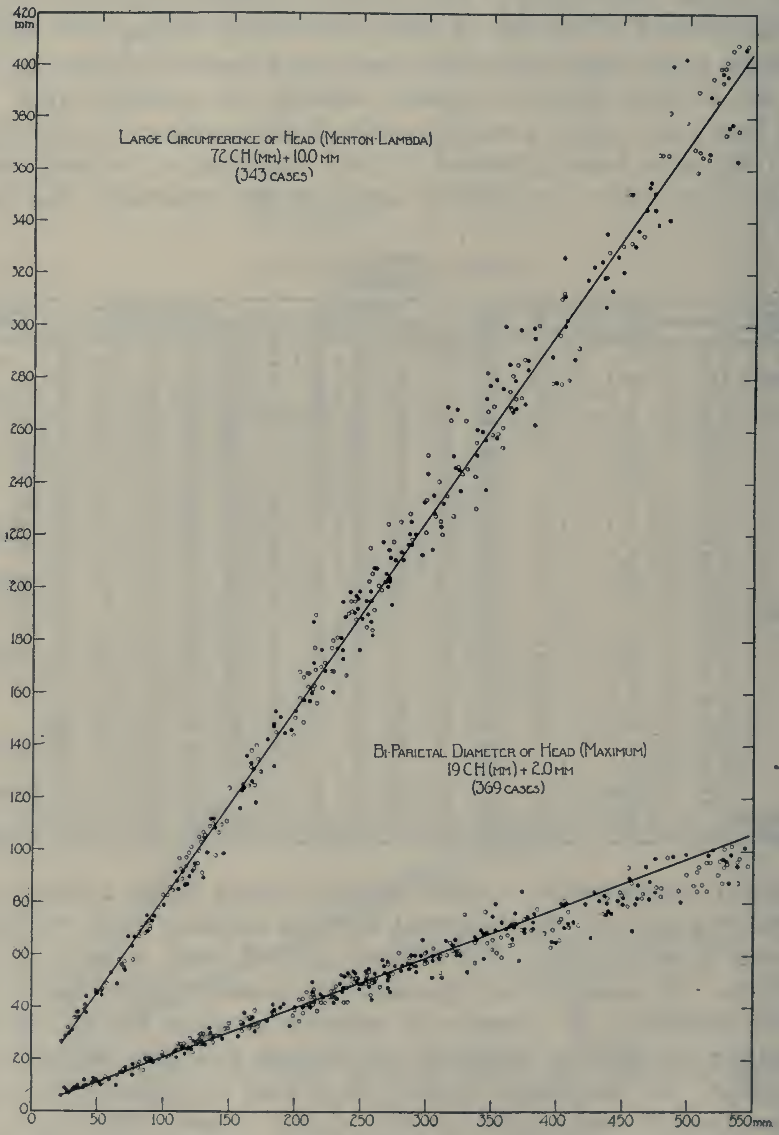


Fig. 6.

Primary injection, on the other hand, produces a much more notice-

TABLE XIII

	AVERAGE FRESH (MM)	AVERAGE END 6 MOS. (MM)	AVERAGE PER CENT CHANGE
C H	263	261	– 0.8
C R	178	178	– 0.4
O F	65	65	– 1.0
Bi P	49	48	– 0.9
So B	59	60	+ 0.4
S O F	63	64	+ 0.7
O M	62	62	+ 0.1
H H C	183	186	+ 1.4
S O B C	181	184	+ 1.6
S O F C	174	179	+ 2.5
O M C	172	174	+ 1.2
L C	190	190	– 0.3

able change. Here again the immersion, following the injection, produces but little effect. Twenty-six specimens were employed in this study and individual variation, while slightly more marked, was due more to the amount of fluid injected than to any other factor. About 30 per cent of body weight seems to be the optimum amount of fluid to use. The size of the specimens seems to make little, if any, difference in the amount of percentage change produced in the head measurements except that the previous condition, in utero, seems to act as a sort of natural limit to the swelling process. The results of this study are shown in Table XIV.

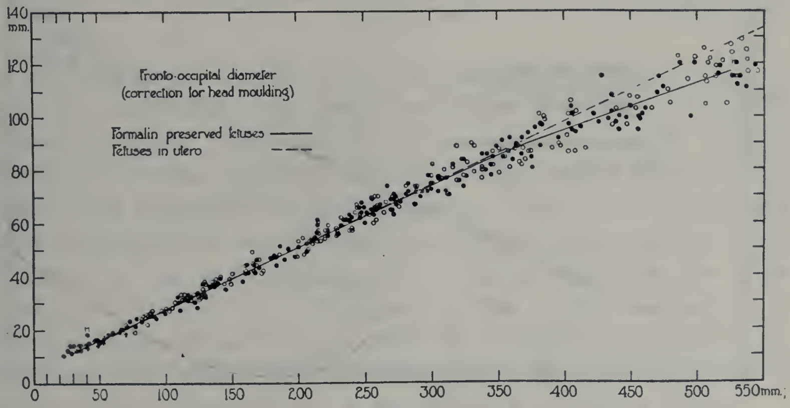


Fig. 7.

While these results show essentially negative changes for body length, they are distinctly positive for the head measurements. If the resulting correction be applied to the original curves for Figs. 1 to 6, the resulting curves would occupy the position shown by the dotted line in Fig. 8. Such a set of curves would properly represent the head proportions for one or several stillborn fetuses.

This injection and preservation study revealed another fact of importance, namely, a peculiar edematous swelling of the tissues of

TABLE XIV

	PERCENTAGE CHANGE FROM INJECTION	PERCENTAGE CHANGE AT END OF 6 MOS. PRESERVATION
C H	+ 1.2	+ 0.8
C R	+ 1.6	+ 0.5
O F	+ 2.6	+ 2.6
Bi P	+ 4.4	+ 3.9
S O B	+ 3.8	+ 3.9
S O F	+ 4.3	+ 4.9
O M	+ 4.8	+ 2.9
H H C	+ 3.8	+ 4.5
S O B C	+ 4.6	+ 4.8
S O F C	+ 5.1	+ 6.1
O M C	+ 7.7	+ 7.4
L C	+ 5.4	+ 5.0

the ischiorectal fossa with a consequent protrusion of the perineum. This protrusion was found to account for the upward deflection in Fig. 1 because the crown-rump measurement had been taken to the perineal surface instead of to the tubera ischii and a technical error thereby introduced. When properly corrected this curve resulted in a straight line, indicated by the straight line in Fig. 1. The fact that injected specimens, in which the effects of birth moulding have been totally or partially obliterated, approach very much more closely to a central, straight line than do fresh, stillborn fetuses, suggested the above mentioned study of unmoulded heads. For this purpose babies born by cesarean section, elective, or very early after the initiation of pains, and those born by breech extraction were utilized. Of the total number of these cases (33), twenty-seven were selected as representing full term infants, they having been born within two weeks of term, according to the menstrual history.

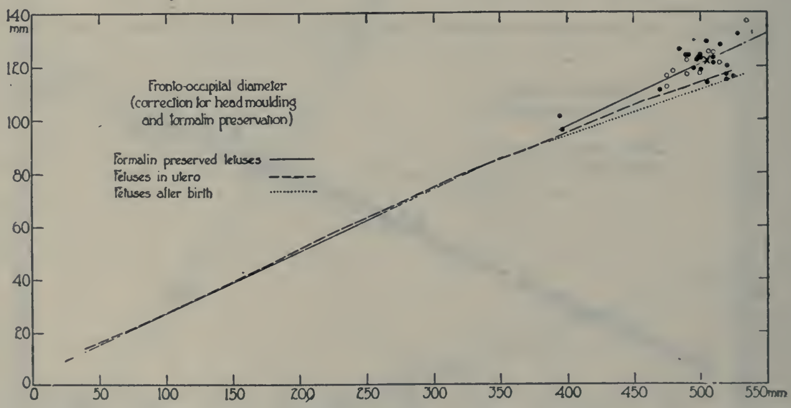


Fig. 8.

The separate readings of this series of measurements appears in

Table XII. These measurements, plotted by the same method outlined above, all fall well above the curve for preserved material (Fig. 8). In fact the average point* of the 27 selected cases, in the case of each dimension, falls directly (within 1 mm.) in the continuation of the lower straight portion of the curve (broken line Fig. 7 and solid line Fig. 8). We have then, by the removal of artifacts, found that all these "curves" are straight lines. These straight lines are shown collectively in Fig. 9 and individually in relation to the field graphs of preserved material in Figs. 1 to 6 inclusive. This would indicate that the fetal head, in relation to body length, has a perfectly definite rate of growth throughout fetal, not including embryonic, life.

These curves, being straight lines, can be expressed by the formula: $y=ax+b$ where (y) is any given measurement, (x) the standing height, and (a) and (b) are constants. For the various measurements these formulae are:

Sitting height	.66	(C H)	+ 5.0 mm
Occipito-Frontal Diameter	.235	‘‘	+ 4.0 ‘‘
Biparietal ‘‘	.19	‘‘	+ 2.0 ‘‘
Suboccipito-Bregmatic ‘‘	.2	‘‘	+ 6.0 ‘‘
Suboccipito-Frontal ‘‘	.215	‘‘	+ 7.0 ‘‘
Occipito-Mental ‘‘	.235	‘‘	+ 2.0 ‘‘
Horizontal Head Circumference	.675	‘‘	+ 13.0 ‘‘
Suboccipito-Bregmatic ‘‘	.625	‘‘	+ 16.0 ‘‘
Suboccipito-Frontal ‘‘	.65	‘‘	+ 15.0 ‘‘
Occipito-Mental ‘‘	.63	‘‘	+ 9.0 ‘‘
Large ‘‘	.72	‘‘	+ 10.0 ‘‘

The constant positive value of (b) in each formula would seem to indicate that, previous to the period at which this study began (23 mm. standing height), the head dimensions gained a certain number of millimeters on the body as a whole, as represented by the standing height, and retained that lead throughout fetal life. This mathematically substantiates our previous ideas of the comparatively early development of the head (Jackson[24]). Similar formulae for other dimensions of the body (as developed in this study) enable one to construct an entire fetus at any period of development, if given any single dimension. Moreover any measurement of the body is just as valuable in determining age as is the standing or sitting height.

From the practical standpoint, one may arrive at the size of the fetal head *in utero* if he can accurately determine the size of any dimension of the body. A moderate number of clinical demonstrations of this indirect method of mensuration have been made and a definite x-ray technic is being developed for this purpose at the present time. Further descriptions of the details of the technic employed and the

---

*The average values of fetal head measurements *in utero* present a rather new idea of the size and proportions of the obstetric passenger and are probably of more clinical importance, in some respects, than the postnatal values quoted in the text-books.

results obtained will be given when a conclusive series of measurements has been completed.

SUMMARY AND CONCLUSIONS

1. Measurements of the head, *in utero,* plotted as ordinates against standing heights as abscissae for any group of Caucasian fetuses, result in straight line curves. (This is also true of measurements of other parts of the body.)

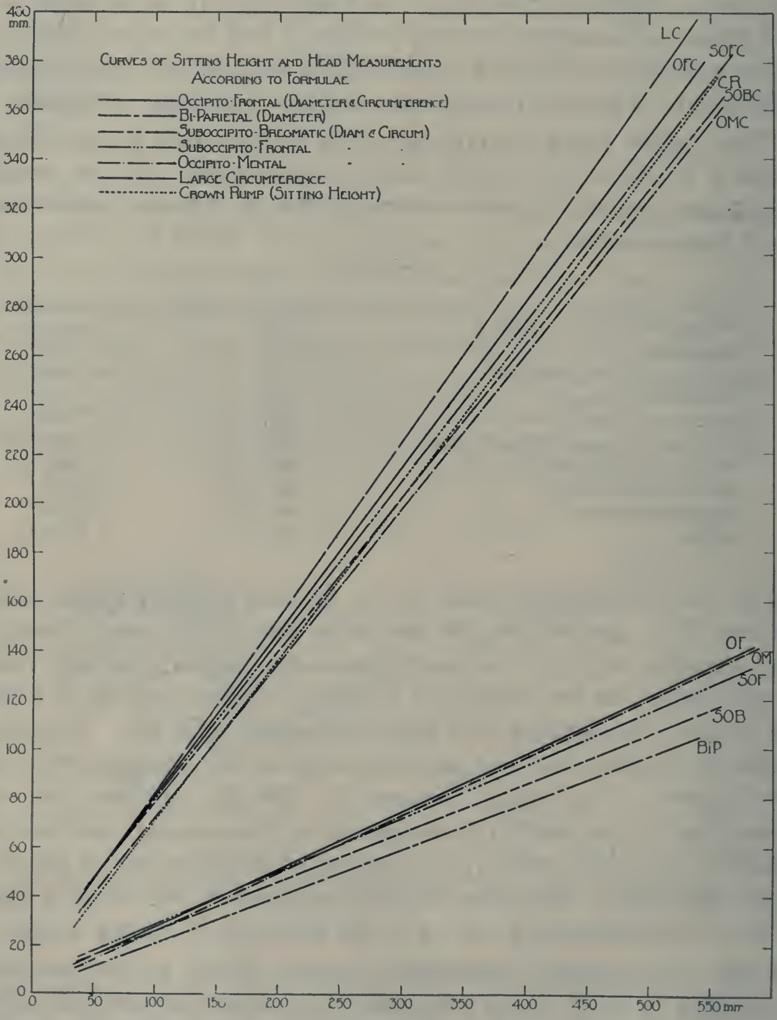


Fig. 9.

2. The relationship between any two dimensions can, then, be expressed by the straight-line, empirical formula: $y = ax \pm b$, (x) and (y) being body dimensions, and (a) and (b) constants.

3. By study of these formulae we find definite mathematical proof of development in the cephalocaudad direction during embryonic life and,

4. A definite rate of growth, in any dimension, established by the third month and maintained throughout the remainder of prenatal life.

5. By the aid of these formulae, one may accurately construct the external body proportions of a fetus at any period of development, if given any single dimension.

6. Likewise, one may deduce the size of the head if one can accurately determine any body measurement *in utero.* A definite technic for this indirect intrauterine cephalometry is worthy of prolonged intensive study. By such a method one could solve problems of disproportion between passage and passenger, as well as determine viability and maturity with a considerable degree of accuracy.

7. Birth moulding probably effects greater changes in head dimensions than ordinarily thought.

8. Fetuses preserved in formalin, by the method outlined, better represent the living fetus *in utero* than any other available type of material.

BIBLIOGRAPHY

(1) *Arnovljevic:* 1884, Das Alter, die grössen und Gewichtsbestimmungen der menschlichen Föten, Diss. München. (2) *Ballantyne, J:* Edinburgh Med. Jour., 1890, xxxvi, 97-112. Lancet, Jan. 26, 1901. (3) *Beneke, M.:* Die Bedeutung einzelner Merkmale zur Altersbestimmung des neugeborenen Kindes. Diss. Leipzig, 26 pp., 1913. (4) *Bouillet:* Montpellier Record Med., 1888, x, 101-115. (5) *Brandt:* Alter Grösse und Gewicht der Fötalorgane des Menschlichen Fötus. Diss. München, 1886. (6) *Budin, P.:* De la tête du foetus au point de vue de l'obstétrique. Thèse, Paris, 1876. (7) *Budin, P., and Ribemont, A.:* Compt. Rend. Soc. Biol., Paris, 1879; Arch. de Tocol, vi, 449-87. (8) *Calderini, G.:* Le dimensioni del foeto negli ultimi tre mensi della gravidanza. Diss. Pavia. 1875. (9) *Clarke, J.:* Phil. Trans. Roy. Soc. London, 1786, lxxvi, 122-30. (9a) *Corrado, G.:* Giorn Ass. Napolit. di Med. e Natural, 1899 ix, 34-39, 220-237. (10) *Dardel, P.:* 1896 Sur l'évaluation du diamètre bipariétal du foetus pendant la vie intra-utérine et sur l'absence de rapports entre ce diamètre et les poids du foetus. Thèse, Paris. (Review in Monatsschr. für Geburtshilfe, viii, 328.) (11) *Faucon, A.:* Pesées et mensurations foetales à differents ages de la grossesse. Thèse, Paris, 1897. (12) *Fehling, H.:* Arch. f. Gyn. 1875, vii, 507-30. (13) *Frassetto, F.:* Atti. Soc. Roma d. Antropol., 1909, xiv, 163-196. (14) *Friedenthal, H.:* Allgemeine und spezielle Physiologie des Menschenwachstums. Berlin, 1914. (15) *Gönner, A.:* Ztschr. f. Geburtsh. u. Gynäk, 1895, xxxiii, 1-12. (16) *Haase, C.:* Charité Annalen, 1875, ii, 669-696. (17) *Hamy, M.:* Compt. Rendus Soc. Biol., 1880, xxxii, 92-93, 130-131. (18) *Heckmann, J.:* Ueber das Verhältniss des Kopfes des Neugeborenen zum Kopf der Mutter. Diss. Giessen. (Reviewed in Monatsschr. f. Geb., 1896, vi, 126.) (19) *Herman, G. E.:* Edinburgh Med. Jour., 1890, xxxvi, 451-452. (20) *Heuser, T.:* Ztschr. f. Geburtsh. und Gynäk., 1912, lxx, 381-393. (21) *Hewson, A.:* Med. Exam. Philadelphia, N. S., 1851, vii, 634-637. (22) *Hrdlicka, A.:* Am. Jour. Phys. Anthrop., 1919, ii, 46-60. (23) *Jackson, C. M.:* Am. Jour. Anat., 1909, ix, 119-165. (24) *Jackson, C. M.:* Morris' Human anatomy, 1914, ed. 5, p. 24. (25) *Jellinghaus:* Arch. f. Gynäk., 1896, li, 33-48. (26) *Jousset, A.:* Rev. Méd. Franc. et Etrang., 1877, lvii, 617-625. (27) *Kaznelson, R.:* Klinische Untersuchungen über asymmetrie des Schädels bei Neugeborenen. Diss. München, 1914. (28) *Kjölseth, M.:* Monatsschr. f. Geburtsh. u. Gynäk., 1913, xxxviii, 216-98. (Erganzh.) (29) *Kochs:* Zentralbl. f. Gyn., 1905, xxix, 37. (30) *Labat:* La tête du foetus au point de vue obstetrical. Ref. in Ballantyne Dis. of Infancy, 1881, p. 25. (31) *Lafaille, L. G.:* Quelques mensurations due

foetus. Thèse, Paris, 1893. (32) *La Torre, F.* Ann. di Ostet, 1894, xvi, 264-7. (33) *Le Cudennec, A.:* Du palper abdominal appliqué a la recherche du volume du foetus par rapport aux dimensions du bassin, 1890, Thèse, Paris. (34) *Legou, E.:* Quelques considerations sur le developpement du foetus. Thèse, Paris, 1903. (35) *Lutz R.:* Zentralbl. f. Gyn., 1912, xxxvi, 1577-81. (36) *Lutz, R.:* Zentralbl. f. Gynäk., 1913, xxxvii, 127-30. (37) *Mall, F. P.:* Anat. Rec., 1907, i, 129-40. Also: Keibel and Mall, Human Embryology, i, 180-201. (38) *Meyer, A. W.:* Archiv. f. Entwicklungsmech. 1914, xl, 497-525. (39) *Michaelis, P.:* Arch. f. Gynäk., 1906, lxxviii, 267-88. (40) *Mueller, A.:* Arch. f. Anthropol. N. F., 1910, ix, 53-63. (41) *Pfannkuch, W.:* Arch. f. Gynäk. 1872, iv, 297-310. (42) *Retzius, G.:* Biol., Untersuch., N. F., 1904, xi, 35-76. (43) *Riggs, T. F.:* Johns Hopkins Hosp. Rept., 1904, xii, 421-64. (44) *Runge, G.:* Arch. f. Anthropol., 1891, xx, 303-319. (45) *Schaeffer, O.:* Verhältnisse des fötalen Menschenschädels. München und Leipzig, 1892, xl, 51 pp. (46) *Schultz, A.:* Am. Jour. Phys. Anthrop., 1919, ii, 34-41. (47) *Sergi, G.:* Rev. di. Soc. Biol., 1900, ii, 401-13. (48) *Spiegelberg:* Monatsschr. f. Geburtsh. u. Frauenkrankh., 1868, xxxii, 276. (49) *Spondli, H.:* Die Schädeldurchmesser des Neugeborenen und ihre Bedeutung. Diss. Zürich, 1857. (50) *Stratz, C. H.:* Ztschr. f. Geburtsh. u. Gynäk., 1909, lxv, 36-51. (51) *Streeter, G. L.:* Carnegie Inst. Contributions to Embryology, 1920, xi, (Nos. 49-55), 143-170. (52) *Stumpf, M.:* Arch. f. Gynäk., 1907, lxxxii, 214-35. (53) *Swayne, J. G.:* Brit. Med. Jour., 1867 v, 768. (54) *Taylor, R.:* Am. Jour. Dis. Children, 1919, xvii, 353-62. (55) *Tenon:* Mem. d. l'Institut Nat. d. Sc. et Arts. An. 6, 1796. (56) *Tovo, C.:* Atti. Soc. Roman. Antrop., xi, 27-41. (Rev. in Centralbl. Anthrop., 1905, x, 130.) (57) *Turnbull, W. M.:* Austral. Med. Jour., 1862, vii 185. (58) *von Hecker:* Arch. f. Gynäk., 1877, xi, 348. (59) *von Rittershain, G.:* Oesterr. Jahrb. für Paediatrik., 1870, ii, 149-214. (60) *von Schaetzel, P.:* Ueber den Einfluss des Alters der Mutter und der Zahl der voraufgegangen Schwangerschaften auf Länge und Gewicht der Neugeborenen. Greifswald, 1893. (61) *von Skalkowski B.:* Arch. f. Gynäk., 1890, xxxviii, 500-510. (62) *Weisz, F.:* Pester medic-chirurg. Presse, No. 52, 1897.

(Reprinted from The Military Surgeon for June, 1923)

THE STATICS OF THE HUMAN ARCH WHEN SUBJECTED TO BODY WEIGHT[1]

By HALBERT L. DUNN, M.D., M.A.
First Lieutenant, Medical Reserve Corps, United States Army

(With seventeen illustrations)

INTRODUCTION

THE ARCH of the foot has long been a subject of medical interest. Many investigators have studied the foot particularly from the standpoint of mechanics, to discover whether the arch is a structural unit and to determine how it distributes the loads to which it is subjected. Many surmises have been made as to the type of arch and its functions. Tubby ('12) believes that one should consider the foot as forming half a dome, the astragalus acting not as a keystone but as a reenforcing girder bridging two oblique piers. Jones ('17), on the other hand, believes that the "so-called arches" of the foot are not true arches at all—that there are no piers or keystones; but that the maintenance foot is entirely dependent upon the tone of its muscles and the strength of its ligaments. Between these two extreme conceptions is a host of ideas concerning the mechanical structure of the arch. Most authors are agreed, however, that there are two arches in the foot, a median longitudinal and an anterior or transverse. Anatomically the presence of these two arches is obvious, but their functional existence has been repeatedly questioned.

Although there have been a great many contributions published on the growth, shape and form of the foot as well as on the reactions of the various types of arches, especially the broken arch, there has been comparatively little quantitative work on the functional activity of the arch. Rogers ('19) concluded that the leverage of the arch was of the first order, the ankle joint acting as a fulcrum. Weindenreich ('21), in a comprehensive comparative anatomical study, believed that the longitudinal arch was an actual functioning unit. Bossi ('08) experimented with the skeleton foot and observed changes in the arch with each change of weight. He concluded that the rotation of the calcaneum under weight was the anatomical factor responsible for the lengthening of the arch and the typical pathologic changes. Belvoe ('17) X-rayed the flat feet of three individuals. He then measured the descent of various fixed bony points with and without loads. His cases were too few, however, to throw much light upon the mechanism of the flat foot. Richardson ('08) also X-rayed three cases of flat feet and measured them, with practically negative results. Baisch ('13), in a radiographic study of both normal and abnormal feet subjected to body weight, observed that in the normal foot subjected to weight bearing there occurred a coaptation of the various tarsal and metatarsal bones while in the flat foot there was a separation of these bones. He claimed to be able to diagnose flat foot by this means. Cramer ('13) studied 118 cases of flat foot by X-ray and observed a chronic deforming arthritis of the bones of the tarsus, the chief deformity being located in the neck of the astragalus.

---

[1] Contribution from the Department of Anatomy, University of Minnesota, and the Medical Reserve Corps, Fort Snelling, Minnesota.

Hoffmann ('07) made a statistical study of the relation between the height of the longitudinal arch and the functions of the foot. He found that the height and the shape of the longitudinal arch were of no value in estimating the strength and the usefulness of the feet. By grouping his cases into high, moderate, somewhat low, very low, and absent arch heights, he came to the conclusion that normal feet presented high, medium and low arches in nearly the same proportion as did the feet with weakened arches. The weakness of the longitudinal arch, in fact, rarely resulted in its depression, according to his observations. He believed, therefore, that it was a mistake to consider foot impressions as an aid in the diagnosis of the weak arch and that symptoms of foot weakness resulted because the arch yielded and not merely because it was normally low. Williams ('09) also concluded that arch symptoms were not related to the height of the longitudinal arch. In his series of 300 cases, 39 per cent had anatomically low arches, 51 per cent medium, 8 per cent high, and 2 per cent pathologically high. Weed ('12) also appreciated the fact that low arches are not necessarily pathologic and that visual examination would not reveal the functional potentiality of a given foot. He pointed out the important fact that a lowered and weakened arch does not necessarily mean a painful arch although there is usually a history of pain at some time.

Feiss ('10) studied the reactions of the arch of the foot when subjected to body weight. He measured the height from the tubercle of the navicular or scaphoid bone because this point changed position when the foot supported the body weight. To measure the depression of the arch under weight, he used a measurement afterwards employed by Heiner ('11) and described by following investigators as "Heiner's line." This line was obtained by placing a ruler on two easily located bony points, (*a*) the lower tubercle of the head of the first metatarsal, and (*b*) the posterior inferior corner of the internal malleolus. From this line a perpendicular was erected which passed through the tubercle of the navicular bone. Feiss found in a group of 100 cases that this perpendicular line varied in length from 0, in two cases, to 1 inch, in three cases. He concluded, therefore, that there was a large normal variation and that the physiological increase in the length of this perpendicular line when the foot was subjected to the body weight represented merely a prototype of the anatomical variation of a foot not supporting the body weight. He defines flat foot, therefore, as the position of the bones, resembling that of the bones of the arch in physiologic weight bearing, which does not disappear when the body weight is removed. He estimated the amount of flattening by the ratio of the lowering of the navicular tubercle. Elmore ('13) recommended the use of the "Heiner's line" as a means of determining flat feet for navy recruits.

Holcomb ('13) demonstrated from statistics of the Surgeon General's Office that the enlistments of colored troops showed a far higher percentage of rejections due to flat feet than did the white enlistments. For the period of seven years, 1905–1911, the rejections of the white recruits from this cause averaged about 3.5 per cent and of the colored 5.8 per cent. Obviously the negroes, having normally a lower arch than the whites, were rejected because of a mistake in diagnosis. Mebane ('18) reported the examination of 2,000 negroes; 40 per cent had flat feet in the sense that the tubercle of the scaphoid (navicular) was lower than normal. Most of these cases only appeared flat because of the plantar fat pads and the well-developed foot muscles. Anderson ('16), Muskat ('09), Schüman ('06) and Bradford and Lovett advocated new methods by which the study of the arch can be facilitated. Codman ('11), Merill ('16), Smith ('18), Harris ('14), Ogilvy ('05) and Quenu and Kuss ('11) dealt with the mechanics of the pathologic arch in a more general way.

The following study was undertaken primarily with two objects, (*a*) to obtain knowledge of the arch as a structural unit and a conception of its function in the distribution of the weight placed upon it, and (*b*) to demonstrate some of the essential differences between the normal and the broken arch. The author expresses his indebtedness and gratitude for the valuable suggestions and facilities placed at his disposal by Dr. R. E. Scammon and Lieut. Col. H. H. Rutherford.

MATERIAL

The data obtained for this study were secured from several sources The feet of 109 individuals were studied, 108 males and 1 female. The 109 individuals were separated into five groups. The first group consisted of 30 college students, 29 having normal feet, and one a moderately pathologic arch which had troubled him for about a year. The second group was made up of 50 soldiers, of whom 38 had no symptoms or signs of arch trouble, 2 had definitely pathologic feet showing symptoms and signs of weakness, and 10 had questionably broken arches. Of these 10, 2 were attempting to enlist and gave no history of foot trouble although their arches yielded markedly under body weight, and the remaining 8 (3 of whom were prisoners) gave confusing histories of indefinite trouble, probably in the hope of avoiding fatigue duty. The third and fourth groups consisted of 20 soldiers who had just marched 1,000 miles with full equipment and in military formation. Ten of these were measured on the first day after entering camp and 10 on the third day. The first 10 (third group) were normal. The second 10 (fourth group) were normal except for one soldier who had moderately pathologic fallen arches which had forced him to ride a part of the distance. The fifth group consisted of 9 hospital cases. Three were normal, 2 were questionably pathologic, and 4 were definitely pathologic. This group included the one female measured, whose arches had broken down during pregnancy, and also one individual with rigid arches who was measured two days after the removal of a plaster cast.

METHODS OF COLLECTING DATA

The various linear and areal determinations were collected in two series; the first was taken directly from the foot, the second was obtained from the footprints. The first series of measurements was taken in the following manner. The weight, age, height of the individual and the history of the previous conditions of his arches were recorded. A brief history was taken in each instance. History of previous illness (especially rheumatic fever), foot injury, arch trouble and pain in feet and legs were noted.[1] The estimation of the arch height by "Heiner's line" was then obtained, but this measurement was discarded in preference to the determination of the arch height as the perpendicular distance in centimeters from the tip of the tuberosity of the navicular bone to the floor. Two linear measurements, the medial longitudinal length and the bi-metatarsal width, were obtained by a caliper scaled in millimeters. Since the range of error in measuring with the calipers was about 0.5 of a millimeter no attempt was made to read within the fraction of a millimeter for any linear determinations. The medial longitudinal length and the bi-metatarsal width were obtained with and without the entire body weight upon the arch of one foot.

---

[1] Blodgett ('04), in a report on 1,000 cases of broken arches, showed that in 68.1 per cent pain was present only in the feet and that in 25.9 per cent it existed in both the feet and the lower extremities. In 2.2 per cent of his cases, on the other hand, the pain was entirely in the lower extremities above the feet, and in 3.8 per cent there was practically no pain at all. Foot pain, therefore, was regarded to be the most important subjective symptom to be elicited.

In order to apply the body weight in a uniform manner, the individual was asked to balance himself on one foot. In this way all of the body weight was directed upon the arch in the line of gravity. The reaction of the arch under body weight, therefore, is a study in statics. In such an investigation the ligaments play the stellar rôle in maintaining the integrity of the arch while the muscles take a minor part.

It is true, to be sure, that the muscles of the foot must be considered to a certain extent even in a study of statics. For instance, in the examination of hypertrophied feet it will be shown later in the paper that hypertrophied muscles are relatively unyielding and tend to support the arch even in a static state. Hubscher ('07) has shown that the supposed general weakness of the supinator muscle groups in cases of flat foot did not exist. He maintained that the flexor hallucis longus was the only supinator clinically insufficient and atrophied in cases of flat foot. Brown ('12) claims that in the static position of the weight-bearing arch the adductor muscles applied their force not at their insertion but at the internal malleolus and the sustentaculum tali, thereby tending to correct pronation. Katzenstein ('14) submits positive proof of the major rôle played by the ligaments in flat foot. He injected ½ to 1 c.c. of weak formaldehyde solution into the plantar ligaments and after holding them in place for three weeks by means of a plaster cast, he found that the relaxed ligaments had been shortened and that the flat foot was functionally normal. Generally speaking the integrity of the ligaments rather than the muscles is being tested when the arches are subjected to static loads.

Footprints were taken for each foot with and without body weight upon the arch. For the footprints, quick-drying, black printer's ink was used. This was spread in a thin film upon the sole of the foot with a rubber roller, and the foot was then placed carefully upon a sheet of smooth finished calendar paper. Impressions were taken with and without the body weight upon the arch. In each case the fixed bony points previously located by ink upon the skin were accurately indicated upon the footprint. In this manner six bony points were projected upon the paper from which measurements could be taken.

The second series of determinations, both linear and areal, was obtained from the footprints themselves.

The linear measurements were made accurately to the nearest millimeter. They were all taken with reference to the fixed bony points which were indicated upon the footprints.

The areal determinations were obtained by means of the planimeter. They are expressed in values of square centimeters and are accurate to 1 square millimeter.

The group of 30 students were studied not only by the addition of body weight upon the arch but also by placing additional loads upon the back. The first weight was 32 pounds, the second 64 pounds. The additional load was obtained by placing on the shoulder a sack containing the respective weights. In all cases footprints and linear measurements were taken as previously described.

The lineal and areal measurements determined were as follows:

(*a*) *Lineal measurements directly on the foot.* (Fig. 1.)

1. H. T.: Heel-toe length; from the most posterior point on the heel to the tip of the great toe.

2. M. L.: Medial longitudinal length; the distance from the lower tubercle of the head of the first metatarsal bone to a point on the perpendicular line on the medial side of the heel which marked the position of the posterior inferior corner of the internal malleolus.

3. B. M.: Bi-metatarsal length; from the lower tubercle on the head of the first metatarsal bone to the head of the fifth metafarsal bone.

(*b*) *Linear measurements taken from the footprints.*

4. A. D.: Anterior diameter; the width of the footprint between the medial and the lateral anterior points. The medial anterior point indicates the location of the lower tubercle of the head of the first metatarsal bone. The lateral anterior point indicates the position of the head of the fifth metatarsal bone.

5. P. D.: Posterior diameter; the width of the footprint between the medial and lateral posterior points. The medial posterior point indicates the position of the posterior inferior corner of the internal malleolus. The lateral posterior point shows the location of the posterior inferior corner of the external malleolus.

6. L. Ax.: Long axis; the length of the footprint between the heel point and the anterior border of the ball of the foot where it meets the great toe. The heel point is the most posterior point of the heel from a line drawn through the two posterior points. These points indicate the position of the inferior posterior corners of the internal and external malleoli.

7. S. Ax.: Short axis; the length of the footprint between the heel point and the anterior border of the ball of the foot where it is closest to the little toe. The heel point is the most posterior point of the heel from a line drawn through the two posterior points.

8. M. A. L.: Medial arch length; the length from the medial anterior point to the medial posterior point. The medial anterior point indicates the location of the lower tubercle of the head of the first metatarsal

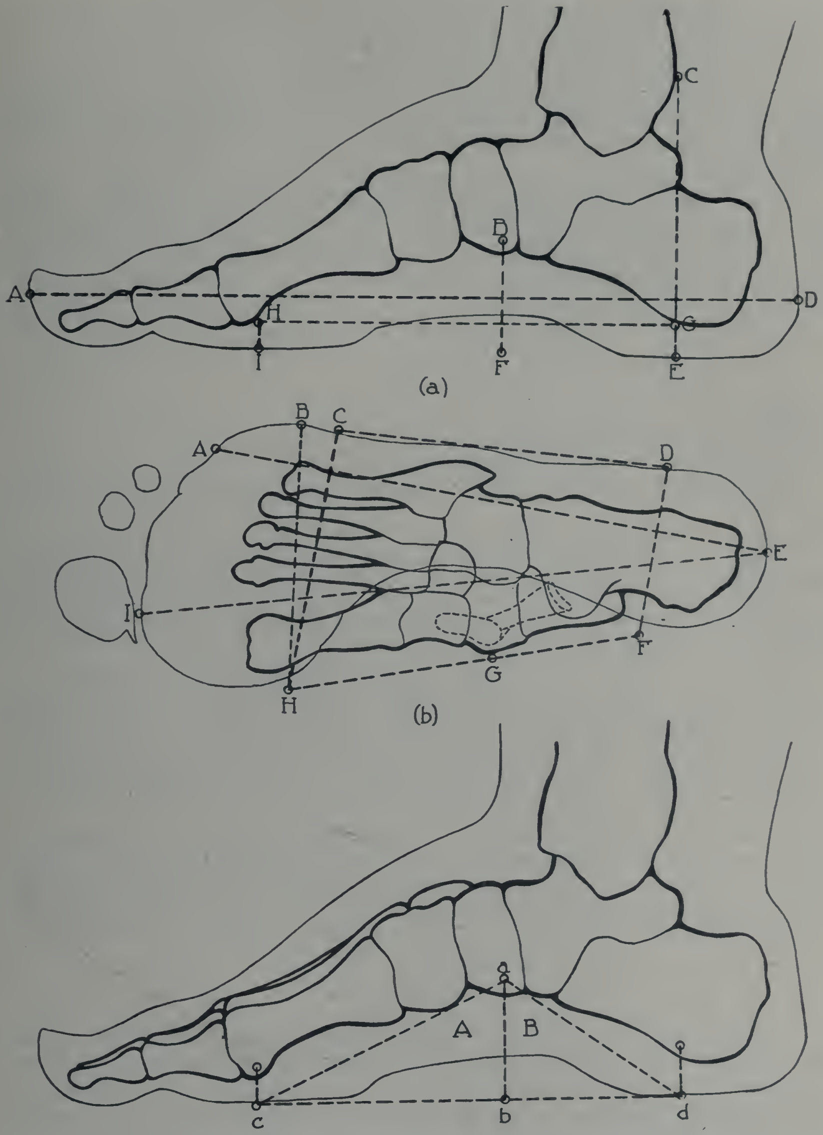


Fig. 1.—Diagram to show the linear and areal determinations which were made.

(a) Medial view; (*AD*) heel toe; (*CE*) the line dropped from the posterior corner of the medial malleolus; (*HG*) medial longitudinal; and (*BF*) arch height.

(b) Inferior view; linear measurements are (*HB*) bimetatarsal; (*HC*) anterior diameter; (*FD*) posterior diameter; (*EI*) long axis; (*EA*) short axis; (*FH*) medial arch; and (*FG*) heel arch length; areal measurements; anterior to line (*CH*), anterior area; posterior to line (*FD*), posterior area; and between lines (*HC*) and (*FD*), middle area.

(c) Medial view; (*A*) anterior triangle; (*B*) posterior triangle; (*db*) heel arch length; (*dc*) medial longitudinal length; and (*ab*) arch height. (Figures modified from Holcomb, '13.)

bone. The medial posterior point shows the position of the posterior inferior corner of the internal malleolus.

9. L. A. L.: Lateral arch length; the length from the lateral anterior point to the lateral posterior point. The lateral anterior point indicates the location of the head of the fifth metatarsal bone, and the lateral posterior point shows the position of the posterior inferior corner of the external malleolus.

10. H. A. L.: Heel arch length; the length from the medial middle point to the medial posterior point. The medial middle point represents the location of the tubercle of the scaphoid (navicular) bone. The medial posterior point indicates the position of the posterior inferior corner of the lateral malleolus.

(*c*) *Areal measurements taken from footprints.*

11. A. B. T.: Area of the big toe.
12. A. S. T.: Area of the second toe.
13. A. T. T.: Area of the third toe.
14. A. Fo. T.: Area of the fourth toe.
15. A. Fi. T.: Area of the fifth toe.
16. A. A. T.: Area of all the toes, viz., the sum of 11, 12, 13, 14, and 15.

17. A. A.: Anterior area; the area of the ball of the foot anterior to a line drawn between the medial and the lateral anterior points. The medial anterior point fixes the location of the lower tubercle of the head of the first metatarsal. The lateral anterior point indicates the location of the head of the fifth metatarsal.

18. M. A.: Middle area; the area of the sole of the foot lying posterior to the boundaries of the anterior area, and anterior to a line drawn between the medial and lateral central points. The medial central point represents the location of the tubercle of the scaphoid (navicular) bone. The lateral central point indicates the position of the tip of the tuberosity of the fifth metatarsal.

19. P. A.: Posterior area; the area of the heel of the foot lying posterior to the line drawn between the medial and lateral central points. The medial central point indicates the scaphoid (navicular) tubercle and the lateral central point locates the tip of the fifth metatarsal.

20. T. A.: Total area; the sum of 16, 17, 18 and 19.

TREATMENT OF DATA

The accuracy of the measurements taken depends upon the nature of the linear and areal determinations and upon the methods employed in taking these measurements. But the significance and the practical value of these data can be ascertained only by the application of statistical and mathematical methods of analysis. The methods used in the study were 8 in number: (1) grouping of all cases in 4 ways—(*a*) by symptoms of weakness, (*b*) by arch height, (*c*) by body weight, and (*d*) by age; (2) calculation of the arithmetic averages of all absolute linear and areal determinations; (3) calculation of the average per cent of change in all linear and areal determinations when the foot is subjected to body weight; (4) calculation, in a group of 60 cases, of the averages of the absolute linear and areal determinations, and of the per cent of change in these measurements when the foot was subjected to body weight plus the additional loads of 32 and 64 pounds respectively; (5) calculation in the same group of 60 cases of the average absolute increments of areal determinations when the foot was subjected to body weight with the additional loads of 32 and 64 pounds; (6) estimation of the force in pounds, the distribution of force in terms of the per cent of total force and the stress in pounds per square centimeter upon the anterior, middle and posterior parts of the foot when the foot was subjected to weight; (7) computation of the absolute and percentage decrease of the arch height when the arch of the foot was subjected to weight; (8) construction of graphs and figures to illustrate the change in the arch height under load and the distribution of weight placed upon the arch to the various parts of the foot. A more detailed description of the application of these methods is given in the following paragraphs.

1. The 109 individuals were classified in four ways; by symptoms or history of arch weakness, by high or low arch heights, by body weight and by age. The symptomatic arrangement of the 109 cases may be expressed in tabular form and falls into six subdivisions as follows:

Group I. (*a*) Normal feet of college students (29 cases).
Group I. (*b*) Normal feet of soldiers (41 cases).
Group II. Hypertrophied feet of soldiers twelve hours after a 1,000-mile march (10 cases).
Group III. Hypertrophied feet of soldiers seventy-two hours after a 1,000-mile march (9 cases).
Group IV. Questionable pathologic flat feet with symptoms but without obvious physical signs or invalidism (12 cases).
Group V. Moderately pathologic flat feet with symptoms, signs and some degree of invalidism (7 cases).
Group VI. Rigid feet two days after removal of cast (1 case).

Group I, containing 70 normal cases, is rearranged according to the height of the arch. The arch heights, the distance of the tuberosity of the navicular bone from the floor, ranged from 2.8 centimeters to 5.4 centimeters and they were separated into groups, each 4 millimeters in range. Group I was also rearranged according to the age of the soldier, in order to see if any correlation existed between increasing age and linear or areal determinations. Finally, the entire group of cases was reclassified on the basis of body weight. The body weights of the 109 cases ranged from 110 to 198 pounds, and this range was divided into nine intervals of 10 pounds each. In order to appreciate the effect of the various symptomatic groupings upon the body-weight classification, the various groups were incorporated into the classes arranged according to body weight. Five tables were constructed to show the relation between body weight and linear and areal determinations. In each instance the cases were separated, as stated above, into nine groups of 10 pounds range, each within the general range of 110 to 200 pounds. The first table included only the 70 normal cases of the symptomatic classification (group I); the second, groups II and III, consisted of the 19 cases of hypertrophied feet; the third was based upon groups I, II and III; the fourth on groups IV, V and VI, and the fifth included all groups. For purposes of analysis of the effect of body weight upon the change in linear and areal determinations of the feet, the fifth table, including all normal and abnormal cases, was found to be satisfactory.

2. The arithmetic averages of all absolute linear and areal determinations were calculated. This process needs little explanation since the average is a method ordinarily employed to find the central tendency of data. The absolute averages were obtained for each symptomatic group with and without the body weight upon the foot. They were also secured for the weight and the age classifications, but only when the foot was not subjected to the body weight.

Calculation of the arithmetic averages of all areal determinations was obtained for each of the symptomatic groups as well as for the arch height and the body weight classifications. In each instance the averages were obtained both when the foot was resting and when it was subjected to body weight. However, the arithmetic averages of the areal measurements for the arrangement of the normal cases according to age, were carried out only for determinations made on the resting arch.

3. The average per cent of change was calculated for each linear and areal determination when the foot was subjected to body weight. The per cent of the change in length under a given load was computed in order to secure a common basis for the study of the expansion of the foot in its various dimensions. The increment was first obtained by subtracting the original absolute length or area from the secondary linear or areal determination when the arch height was subjected to the body weight. The percentages that these absolute increments formed of the secondary linear or areal determinations were then averaged. This average served as an index of the reactions of the foot under the body weight. It is necessary at this point to explain the difference between the average of the per cent which has been described above, and the per cent of the average absolute linear measurements, which has an entirely different meaning. A simple example illustrates the difference between them.

	A	*B*	*Per cent* *C*
	3	2	66
	2	3	150
	5	4	80
Average........	3.33	3.00	99

Let column *A* represent absolute values and column *B* the increments. The per cents, which the increments form of their absolute values, are indicated in column *C*. The average is 99 per cent. Since each of the per cents which make up this average represents a real value, the average of the per cent is also a real value: If, on the other hand, one takes the per cent which the average of the increments, column *B*, forms of the average of the absolute numbers, column *A*, the answer is 90 per cent. This is a per cent of an average and is an artificial measure. It has no direct relationship with the natural variation of the data itself. Throughout this paper the average of the per cents was always used.

4. The averages of the absolute linear and areal determinations and the averages of the per cents of the increments were calculated in a group of 60 college students, group I (*a*), when additional loads of 32 and 64 pounds, respectively, were placed upon the foot. The methods were identical with those already described.

5. The average absolute increments caused by the addition of the body weight upon the arch were calculated for all linear and areal determinations and recorded in tabular form. In the case of the 60 college students, the increments of both absolute and areal measurements were obtained, after each additional load was put upon the back, and incorporated in special tables.

6. The force in pounds, the distribution of this force by the arch, and the stress in pounds per square centimeter upon the various parts of the foot were next determined. In each case the force acting upon the foot as a whole was known. Given the body weight, how is it possible to split it up into component parts which go to the anterior, middle and posterior parts of the foot respectively? This cannot be done from the absolute areal determinations because they are not caused by the body weight. The absolute increments of the various areas, however, are due entirely to the force acting upon the arch. Since this is true, it is logical to assume that if the absolute increment of the total area of the foot is caused by the body weight acting upon the arch, the absolute increment of the anterior area of the foot for instance would be caused by that portion of the body weight acting upon the anterior part of the foot. The per cent of the total force to the anterior area of the foot can be expressed by the simple equations:

$$\frac{\text{Increase in total area}}{\text{Total force}} = \frac{\text{Increase in anterior area}}{\text{Force going to the anterior area}}$$

and, solving,

$$\text{Force to the anterior area} = \left[\frac{\text{Increase in anterior area}}{\text{Increase in total area}}\right] \text{Total force}$$

The per cent of the total force going to the toes cannot be calculated by this formula. The increment of the toe area when weight is applied is relatively enormous. The increment in the toe area under increased weights is caused mainly through the action of the muscles of these structures and not by the increased pressure thrown upon them. In all probability only a very small per cent of the total force on the foot is transmitted to the toes. Since the small amount of the total force going to the toes could not be accurately determined, it was omitted in the estimation of the approximate distribution of the force to the anterior, middle and posterior areas of the foot respectively. This distribution was calculated by the formula described above. The increment of the total area caused by body weight acting upon the foot was determined by adding the increments of the anterior, middle and posterior areas.

After the distribution of the force was determined in per cent of the total force for the anterior, middle and posterior areas respectively, the actual force to each respective area could be easily calculated by multiplying the per cent of the total force by the total body weight as explained above in the formula.

The stress, or the weight per unit of area, was calculated by dividing the force acting upon the anterior part of the foot, for example, by the area of this region. The pounds per square centimeter or stress which is obtained in this manner is a true index of the distribution of the body weight upon the various parts of the foot.

The force and stress upon the anterior, middle and posterior areas were calculated for each of the symptomatic groups as well as for the arch height and the weight classification.

7. The absolute and percentage depression of the average arch height was investigated when the foot was subjected to known loads. Actual measurements of the decrease in arch height due to weight is a difficult procedure. The navicular bone does not sink directly under the load but rotates slightly medially and downward. The entire foot can be either pronated slightly or everted in an effort of the individual to balance his weight. This changes the arch height and makes it difficult to measure. The depression can be calculated, however, by a simple theorem of geometry, viz., that the sum of the squares of two sides of a right triangle is equal to the square of the hypotenuse. By a glance at Fig. 1 (*c*), it can be observed readily that the longitudinal arch of the foot is made up of two right triangles A and B. The line ab represents the arch floor height or, in other words, the perpendicular distance from the tubercle of the scaphoid bone to the floor. The line bd indicates the heel arch length or the distance from the projected points of

the tubercle of the navicular (scaphoid) and the posterior inferior corner of the internal malleolus. The line *cd* represents the medial arch length or the distance from the inferior corner of the internal malleolus, which was projected upon the footprint to the base of the first metatarsal. It is obvious, therefore, that the heel arch length subtracted from the medial arch length gives a value for the line *cb*. The values of *cb* and *ab* are now known, and the value *ac* or the hypotenuse of the right traingle *A* must be obtained. To do this the theorem of squares was applied.

$$(cb)^2 + (ab)^2 = (ac)^2$$

Solving this equation the value of *ac* is obtained.

$$(ac) = \sqrt[2]{(cb)^2 + (ab)^2}$$

where the values *ac*, *cb* and *ab* represent average measurements upon the normal or abnormal foot not subjected to weight.

When the weight of the body is put upon the arch two changes take place; first, the arch height becomes depressed; and second, the heel-toe length and the medial longitudinal length increase. This is shown by the averages of the two linear measurements with weight upon the arch. The heel arch length and the line *ac* are constant, as will be proven later, and do not change when the body weight is placed upon the arch. This is probably due to the bony supports—the calcaneous and the metatarsals. Since the line *ac* does not change in length, all the increase in the heel toe length must occur in the line *cb*. Likewise the arch height must be lowered as the line *cb* is lengthened. The increase in length of *cb* due to the body weight is determined by actual measurements. The new value of the arch floor height when the arch is subjected to the body weight can then be calculated by the expression:

$$(ab) = \sqrt[2]{(ca)^2 - (cb)^2}$$

in which *ab* is the new arch height, *ca* is the constant distance already determined from the tubercle of the scaphoid to the tubercle of the first metatarsal, and *cb* is the variable distance which has been actually measured from the tubercle of the first metatarsal to a perpendicular line projected downward from the tubercle of the scaphoid.

8. Figures were constructed to illustrate the change in the arch height under loads. Graphs were made likewise to point out the most important stresses upon the anterior, middle and the posterior parts of the foot under various conditions.

DISCUSSION OF RESULTS

The observations and discussion which follow are based upon collected data and upon the tables, graphs and figures which have been calculated and prepared by the methods just described.

Since the discussion covers a number of rather divergent results, it is divided for convenience into fourteen subdivisions as follows: (1) A classification of the etiology of flat foot; (2) the relation of the body weight to average linear and areal measurements and the increments of these absolute determinations, the force, the distribution of the total force and the stress upon the surface of the foot when it is subjected to body weight; (3) the relation of the body weight to the incidence of flat foot; (4) the relation of age to the absolute linear and areal determinations of the normal foot when not subjected to body weight; (5) the relation of age to the incidence of flat foot; (6) the relation of the arch height to the average absolute linear and areal determinations and the increments of these averages, the force, the distribution of the total force, and the stress upon the normal arch when the foot is subjected to the body weight; (7) the comparison of the absolute and per cent decrease in the calculated arch height of the various types of feet, and a comparison of the average absolute and per cent decrease of the normal and the moderately pathologic flat foot under additional loads; (8) a comparison of the average absolute linear and areal determinations and the percentage change of these averages, the absolute increments, the force, the distribution of the force and the stress upon normal and moderately pathologic flat feet when influenced by increasing loads; (9) the comparison of the right and the left foot in absolute and per cent averages, with and without body weight; (10) the comparison of the average absolute linear and areal determinations, of the percentage increase and the absolute increments in these determinations, and of the force, the distribution of the total force and the stress upon normal and abnormal feet when subjected to body weight; (11) the distribution of the force upon the anterior, middle and posterior parts of the foot in terms of per cent of total force; (12) the significance of the stresses upon the various areas of the foot and the rôle played by the bony arch and the tissues in its distribution; (13) the mechanics of the arch of the foot; and (14) the practical significance of the results.

The subdivisions mentioned above will now be considered in greater detail.

1. A classification of the etiology of flat foot necessitates the division of the data into age groups. Below 12 years rickets, fever, and congenital anomalies are the most important factors; above 12 years, fevers, occupational conditions and over weight are largely responsible. Broken arches of children are usually the result of rickets. According to Walsham ('95), rickets caused the broken arches in 96 out of the 103 children whom he examined.

Above 12 years the etiological factors will be considered in approximately the order of their importance.

Trauma and foot strain are proportional to the occupational factors causing them. A twelfth of all the cases of Walsham ('95) and an eighth of all his cases over 24 years of age were caused by sprain. Blodgett ('04), who observed individuals from the laboring class, found trauma to be the cause of flat foot in the majority of his cases. Williams ('09), who examined persons from the middle and upper classes, assigned trauma to fifth place. It is well to remember, however, that trauma as an etiological factor is usually overemphasized by the patient.

Fever and infection should probably be given first place in the incidence of flat foot. Rheumatic fever alone caused one-eleventh of the cases reported by Walsham. Blodgett believed that infection was responsible for one-fifth of the broken arches which he examined.

Wasting illness and debility after long sickness was thought to be an important factor by both Blodgett and Williams.

Weight as a cause will be considered later in the discussion. Tubby, Walsham, and Blodgett emphasized the fact that a sudden increase of weight placed a severe strain upon the ligaments of the foot.

Rickets is of minor importance in the adult.

Time of year is also an etiological factor. The data of both Blodgett and Williams showed that the incidence of flat foot in the spring and summer was at least twice as great as it was in fall and winter.

The significance of sex is disputed and probably depends upon the occupation rather than any anatomical difference between the male and female arch.

2. The growth of the body as indicated by body weight is correlated with the average absolute linear and areal determinations of the foot as well as the absolute increments of these measurements, and it is also related to the force, the distribution of the force in terms of total force, and stress upon the various regions of the foot.

In the body weight classification, as has been described in the preceding pages, the 109 individuals ranging from 110 pounds to 198 pounds were divided into 9 groups of 10 pound intervals. In order to ascertain what effect the various symptomatic groupings (page 19) might have upon the body weight, tables based on the body weight classification were made for different combinations of these groups. Group I, including 70 individuals all having normal feet, is represented in Tables 1 and 2. Table 1 shows the absolute linear and areal measurements when the foot is not subjected to body weight, and table 2 shows the areal determinations when the foot is subjected to body weight. A definite relationship is noticed between the increments in both the linear and the areal measurements and the body weight. The increase is most marked in the longitudinal dimension of the foot, the medial arch length increasing from 11.3 cm. at a body weight of 110 pounds to 13.8 cm., or about 22 per cent at a body weight of 174 pounds. This extremely large increment is probably caused not only by the growth of the foot in the long axis, but also by the greater stretching of the ligaments under the longitudinal arch when a heavier body weight is placed upon the foot. The absolute increments of the areal determinations before and after the body weight was put upon the foot were noted in each of the various areas measured. They ranged from 15 to 60 per cent. Tables 3 and 4 show the linear and areal measurements on Groups II and III—the 19 individuals with hypertrophied feet. In Tables 5 and 6 the results of Tables 1 and 3 and of Tables 2 and 4 have been united in order to estimate the relation of body weight to all the normal foot measurements. Tables 7 and 8, on the other hand, contain the absolute linear and areal determinations of the questionable pathologic foot, the moderately pathologic flat foot and the two rigid arches. Tables 9 and 10 combine the data of all the groups. The variations of groups II, III, IV, V, and VI from the normal cases in group I are largely due to insufficient data in these groups. A comparison of the various curves of the total area, for example (Fig. 2), shows that the curve representing all groups is almost identical with that based on group I. It was concluded, therefore, that the average absolute linear and areal determinations did not differ essentially in the various types of feet when their relation to body weight was obtained; and that a further analysis of these measurements could be safely carried out upon the combined data of all six groups.

The increments in the absolute areal determinations before and after the foot is subjected to the body weight are shown in Table 11. The absolute increments become larger with the increase of body weight, the anterior area and the area of the toes increasing in the same proportion as the body weight. The posterior and total areas do not increase quite as rapidly in proportion to the increase of body weight while the increments of the middle area become only slightly larger under increasing loads. From these observations it is apparent that the middle area of the foot is almost completely expanded by the weight of a light individual, while, on the other hand, the areas of the toes and the anterior part of the foot almost double their increments when subjected to a heavy body weight.

In Table 12 the force in pounds, distribution of the force in per cent of the total force and the stress in pounds per square centimeter were calculated for the same group of cases from which the absolute increments were obtained. These calculations were carried out by the formula previously described:

$$\text{Force to anterior part of foot} = \frac{\text{anterior area}}{[\text{total calculated area}]} \times \text{total force on the foot}$$

The distribution of the force in per cent of the total force is obviously the per cent which the anterior, middle or posterior area forms of the total area. The force to the anterior area, for example, is found by multiplying the total force by the per cent of the force going to the anterior area. The stress is calculated, in turn, by dividing the total force into the anterior area. The distribution or the per cent of force going to the anterior area (Table 12) increases from 16.6 per cent at a body weight of 134 pounds to 18.3 per cent at 173 pounds. The per cent of the total force going to the middle area remains practically the same when the body weight increases, while the per cent which goes to the heel decreases slightly. As the body becomes heavier,

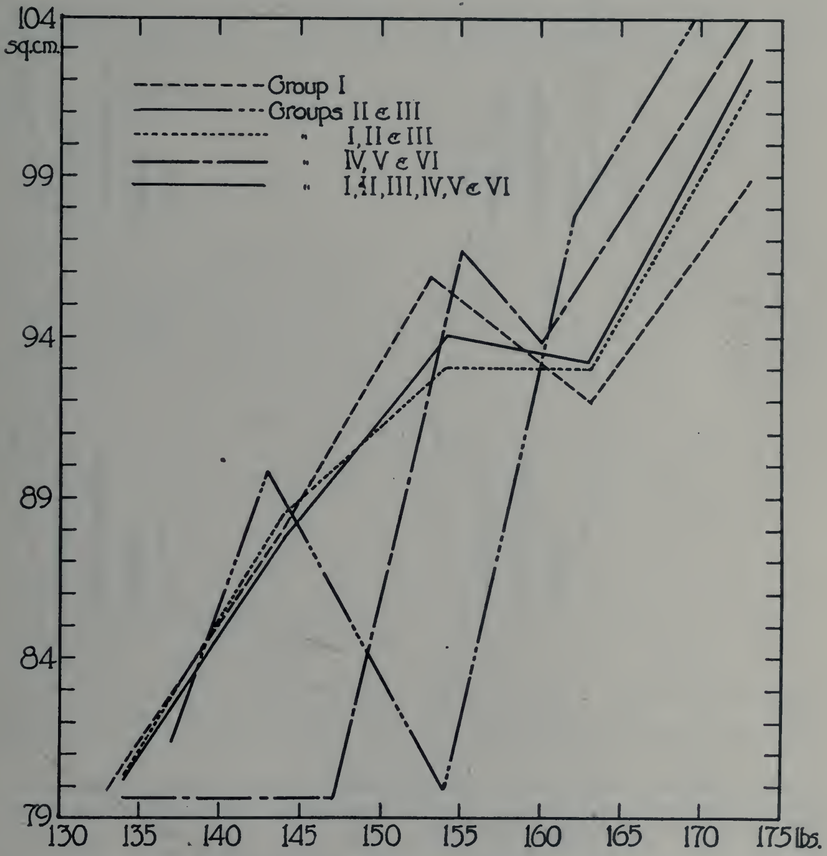


Fig. 2.—Relation of total area (square centimeters) and body weight (pounds).

therefore, a greater per cent of the weight is shifted upon the ball of the foot, and a correspondingly smaller per cent of the weight falling on the arch remains practically constant. The amount of force in pounds to the anterior, middle and posterior areas becomes greater in all cases as the load is increased. The anterior area receives approximately 18 pounds at a body weight of 114 and about 42 pounds at a body weight of 195, the middle area or arch of the foot sustains the greatest bulk in actual weight, ranging from 79 pounds at 114 pounds of body weight to 120 pounds in an individual weighing 195 pounds. The posterior area receives about 17 pounds and 32 pounds at the respective body weights of 114 and 195 pounds. This means that the great bulk of the weight is supported by the middle arch area which also is the largest subdivision of the total area of the foot.

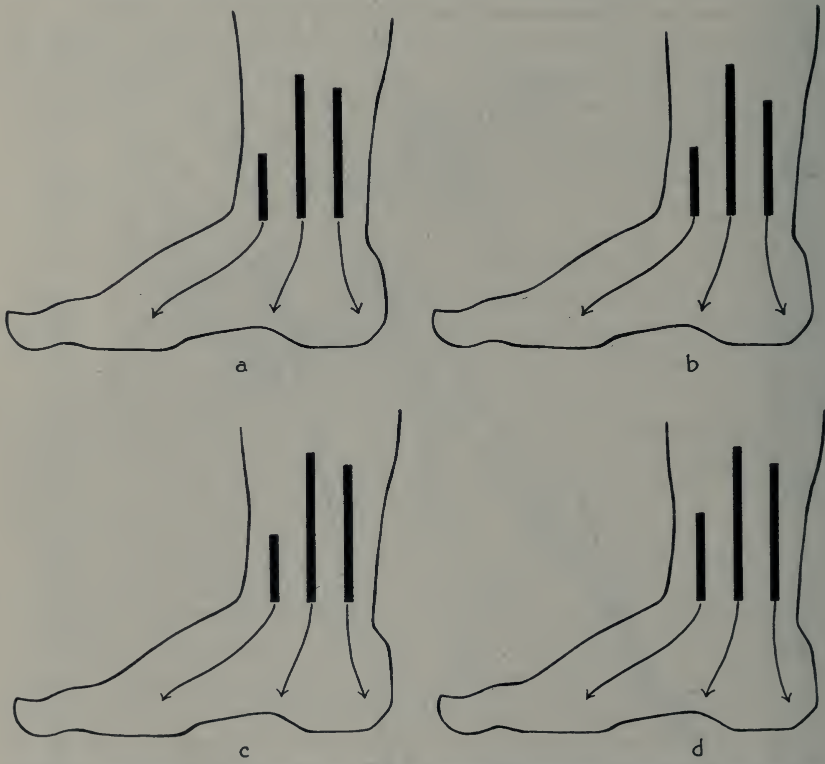


FIG. 3.—Diagrams to show the stress (pounds per square centimeter) acting upon the anterior, middle and posterior areas of the foot; (a) when the foot is subjected to a body weight of 134 pounds, (b) 144 pounds, (c) 154 pounds, and (d) 163 pounds.

The stresses upon the anterior, middle and posterior areas of the foot were obtained by division of the absolute weight by the area in square centimeters to which it is distributed. The results are shown in Table 12 and graphs 3 and 4. The stress on the anterior area rises from 0.68 pound per square centimeter in an individual weighing 134 pounds to about 0.86 in one weighing 173 pounds. The stress of the middle area for the same range of body weight increases from 1.53 to 1.64 pounds per square centimeter, and that of the posterior area, from 1.38 to 1.44. In other words, the stress on the anterior area increases almost 2/10 of a pound per square centimeter when the body weight shifts from 134 to 173 pounds, the stress on the middle area increases not quite 1/10 of a pound per square centimeter, and that of the posterior area only about 1/16 of a pound per square centimeter. This signifies that in an individual of light weight, the heel is taking practically all the weight that it is possible for it to assume, while the anterior part of the foot, on the contrary, is not used for weight bearing to the same degree that it is in a heavy individual.

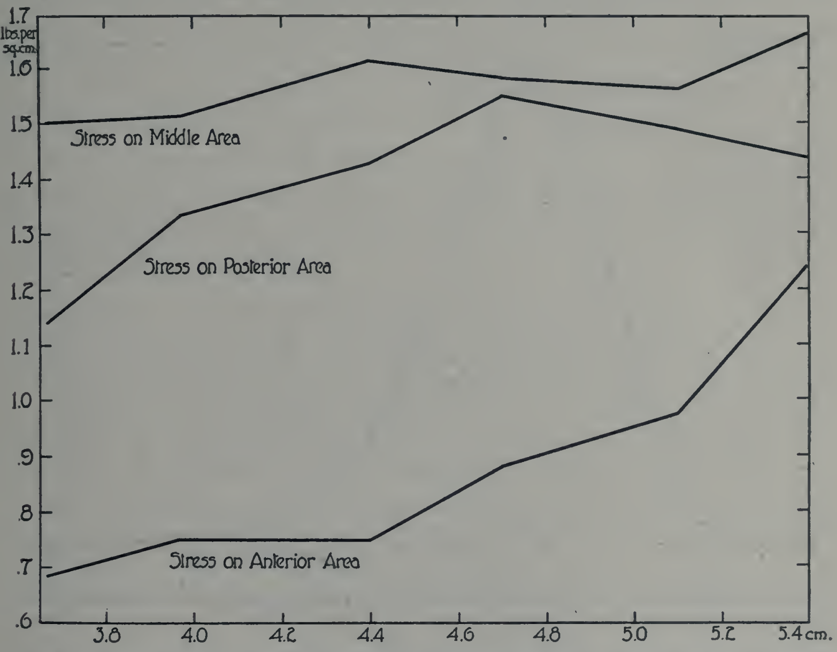


Fig. 4.—The change of stress upon the anterior, middle and posterior areas when the foot is subjected to an increasing body weight.

3. The relation between flat foot and body weight has been discussed by various investigators. Tubby ('12) and Blodgett ('04) emphasized the fact that overweight or a sudden increment of weight was a prime factor in arch trouble. Williams ('09) agreed with them

but believed that weight in itself was not a matter of great importance. United States Army statistics ('20 and '21) proved that men with flat foot were relatively heavy. The average body weight of 867,757 men accepted in the first million draft recruits was 141.54 pounds. Of this number 175,358 were men with flat feet who had an average body weight of 143.24 pounds—a difference between the averages of 1.7 pounds. The average weight of the 692,399 men with normal feet was calculated and found to be 139.84 pounds. The total difference, therefore, between the average body weight of those men with normal arches and those with broken arches was 3.4 pounds. Examination of the data upon the second million draft recruits yielded practically identical averages. The arrangement of the data in the U. S. statistical reports makes it impossible to compare identical distribution of the body weight curves in the two classes of individuals. By shifting to the percentage basis, however, it is possible to demonstrate the difference between the weight distribution of men with normal and abnormal feet. The solid line in Fig. 2 represents the percentage distribution of the body weight of the 867,757 men in the first million draft recruits. The broken line indicates the percentage frequency polygon of the individuals with flat feet. Since the heavy curve includes both normal and abnormal cases the differences shown in the figure are not as striking as they are in reality. The apex of both curves comes at a body weight

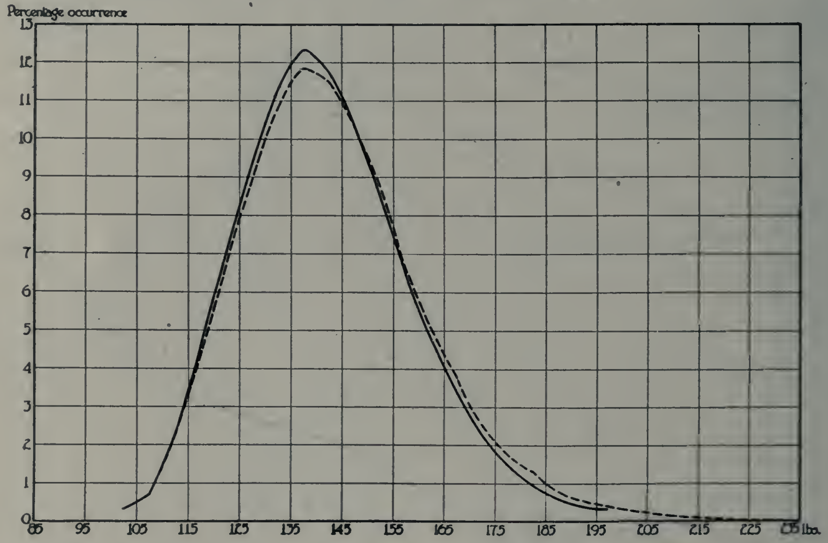


Fig. 5.—Relation of body weight to the incidence of flat foot. Solid line is the percentage distribution curve of normal individuals; broken line, the frequency curve of a group with flat feet.

of 137.5 pounds. Each frequency polygon is skewed to the left because of the selective elimination of those men who are under weight. Above a body weight of 150 pounds, the percentage incidence of men with flat feet is uniformly larger; below, it is smaller. These data prove, therefore, that a correlation exists between body weights over 150 pounds and flat feet. This correlation is not of great importance and is frequently overlooked in a small number of cases.

4. The normal cases constituting the 70 individuals of group I were reclassified according to age in order to see if any relation existed between age and the absolute linear and areal determinations of the normal foot. The results (Table 13) were practically negative. To be sure, the anterior area of the foot seemed to show a steady increase from 27.4 square centimeters at about the eighteenth year to 30.2 square centimeters at the thirty-third year, but there was also a slight gain in the absolute body weight during this period which could easily account for this increase. It is safe to conclude, therefore, that increasing age in the interval from sixteen to thirty-four years has no significant relationship to the absolute linear and areal measurements upon the foot.

5. There is a correlation between age and the incidence of broken arches. The foot of the infant is normally anatomically flat. Comprehensive studies on this matter by Dane ('98), Selter ('00) and Spitz ('04) have shown in general that the arch of the infant is not flat and that the anatomically flat appearance is due largely to a plantar pad of fat. In the adolescent and adult the incidence of the broken arch varies considerably with the class of people under observation. Four principal sets of data (Table 14) are available for reference: Walsham and Hughes ('95), Whitman ('19), Blodgett ('04) and Williams ('09). All of these investigators except Williams carried on their studies among the laboring class of people. Walsham and Hughes examined the arches of 1,078 individuals; Whitman studied 1,000; Blodgett, 974; and Williams, 300. The bulk of Blodgett's cases were over 30 years of age. His data, therefore, were not analagous to those of Whitman and Walsham. The 300 individuals examined by Williams varied greatly from those of other investigators since they were for the most part women from the middle and upper classes. The extremely high incidence of flat feet between 10 and 20 years indicated by the data of Whitman and Walsham, about 50 per cent of the total, undoubtedly signifies the occurrence of the so-called occupational broken arch. This tends to prove the contention of Tubby ('12) that age, in all probability, is correlated with broken arches only to that degree that it is simultaneously associated with occupational factors.

6. After grouping the data according to age and weight, the normal cases were classified according to the height of the arch. Only the averages of the areal determinations were calculated, but these averages were determined for both the resting foot and the foot subjected to body weight.

The absolute areal measurements, Tables 15 and 16, set forth in parallel columns the absolute areas before and after the body weight was applied to the foot. As the arch height becomes greater when the foot is not subjected to body weight, the area of the anterior, middle and posterior parts of the foot become progressively smaller in size. The average body weight remains practically the same, and consequently cannot be the cause of this condition. When the foot is subjected to the body weight, however, the absolute areal measurements of the anterior part of the foot remain practically the same, while those of the middle and posterior areas decrease slightly. The higher the arch, therefore, the smaller is the absolute area of the foot needed to support the same amount of body weight.

The increments of the absolute areal determinations with and without the body weight upon the arch (Table 17) demonstrate the fact that a high arch height more than doubles the increments of the anterior area while it leaves those of the posterior and middle areas practically the same. This means evidently that a high arch throws more of the body weight upon the anterior part of the foot than it does upon the heel. The percentages which the average increments of the various areal determinations form of the absolute areas when the foot is subjected to the body weight are tabulated in Table 15. During the elevation in arch height from 3.7 to 4.7 cm. the toe area is increased 3 per cent and the anterior and posterior areas about 4 per cent, while the middle area decreases approximately 3 per cent. This apparently indicates that, as the arch height becomes greater, the arch itself becomes relatively more rigid while the anterior and posterior areas become more expansible.

The force, distribution of force, and stress upon the anterior, middle and posterior areas of the foot (Table 18) were next computed as described in the section of the paper on methods.

As the arch height increases one centimeter (from 3.7 to 4.7 cm.) the per cent of the total force upon the anterior area rises from 16.4 to 19.5, and the per cent going to the posterior area increases from 13.2 to 16.2, while the per cent upon the middle area drops from 70.5 to 64.2. This indicates that as the arch becomes higher a greater per cent of the total force is thrown anteriorly upon the ball of the foot and posteriorly upon the heel.

The absolute amount of force in pounds upon the foot increases as the arch height becomes greater. In the anterior area it rises from 22.6 to 29.3 pounds, and in the posterior area from 18.2 to 24.4 pounds as the arch increases one centimeter in height. However, the absolute weight upon the arch of the foot remains about the same. The stress in pounds per square centimeter increases steadily in the anterior part of the foot as the arch height is elevated from 0.69 to 0.88 and from 1.15 to 1.55 in the heel (Fig. 6). The stress in the arch of the foot, however, remains about the same, increasing only from 1.5 to 1.59 pounds per square centimeter.

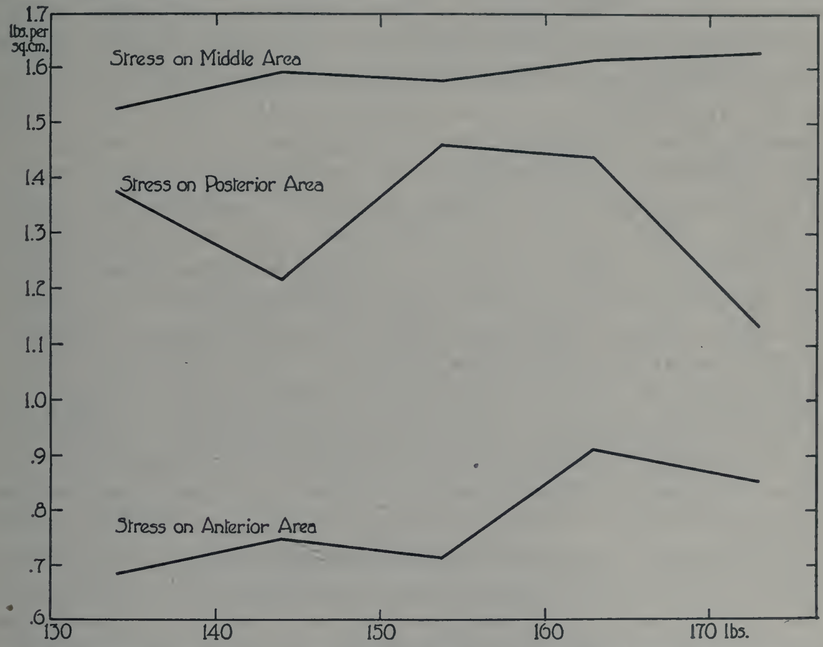


Fig. 6.—The change of stress upon the anterior, middle and posterior areas when the arch height is increasing.

The effect of arch height and the manner in which the low and the high arches distribute force is shown, therefore, by both the per cent of the total force and by the stress upon the middle area of the foot. The force upon the arch area is approximately the same whether the arch be low or high. As the arch becomes higher, however, an increased weight is thrown upon the ball of the foot and the heel, thus keeping the stress upon the arch approximately the same.

7. The effect of arch height was also studied by comparing the absolute and the percentage decrease in the calculated arch height of the various groups of individuals, as well as by comparison of the

average absolute and percentage decrease of the normal and moderately pathologic flat foot subjected to additional loads.

The depression of the arch height in normal and abnormal feet (Table 19) was calculated as described in the section (7) upon methods. In all computations the heel arch length (Fig. 1) was taken as a constant, 4.54 cm. The average absolute observed arch height of all six groups varied less than one-half of a centimeter. The average observed arch height of the normal foot was 4.35 cm. the highest of any group; the rigid arch height was the lowest, 4 cm. The calculated average absolute arch height varied from 3.8 cm. in group II to 0.8 cm. in group V or a range of 3 cm. The range in the calculated arch height of the various groups with the foot subjected to body weight was six times as great, therefore, as the range in the observed arch height in the same groups when the foot was not subjected to the body weight. The absolute depression was obtained for each group of cases by subtracting the calculated arch height from the observed average arch height. The per cent which this absolute depression formed of the original length was also computed. The depression of the normal arch, group I, was 0.62 cm., which amounted to 14 per cent of the original height. The hypertrophied feet of the soldiers, who were measured on the first day after ending a 1,000-mile march, showed an absolute depression of 0.37 cm. and a percentage depression of 8.8. The strong, hypertrophied plantar muscles of these soldiers held their arches practically rigid and unchanged even when the entire body weight was put upon them. The hypertrophied feet of the soldiers, who were measured three days after their 1,000-mile journey, showed a striking change. The absolute depression and the percentage depression of the arch under the body weight were practically identical with those of a normal foot. In three days' time the strong muscles of the foot supporting the arch had changed in their physiological reaction. The size of the muscles under the longitudinal arch still indicated a distinct muscular hypertrophy. Functionally, however, the arch had already reverted to the normal type.

The calculated depression of the arch height in the case of the moderately pathologic flat foot was 3.42 cm. or 80 per cent of its original length. This measurement is by far the most striking difference between the normal and the broken arch. In all cases the moderately pathologic flat foot showed considerable muscle under the longitudinal arch and, therefore, this extreme depression of the arch height when subjected to body weight could not be due to the lack of muscular development. It must be the ligaments, therefore, which limit the descent of the arch in the normal foot. When these ligaments become loosened, attenuated or broken, the arch gives under the body weight regardless of whether the plantar muscles are weak or strong.

A graphic portrayal of these results (Fig. 7) shows the per cent depression of the hypertrophied, normal and moderately pathologic flat foot. The line *BD* represents an arch height of 100 per cent. The line *AB* is a constant and the medial longitudinal length *AC* is also considered to be 100 per cent of that measurement. The per cent of depression of the normal foot increases the medial longitudinal length by *FA*. The enormous depression of the arch height to *JD* which occurs in the moderately pathologic flat foot only increases the medial longitudinal arch by the per cent *EA*. As will be shown later in the discussion, the depression of the high arch has a much greater relative effect than has an equal depression of a low arch. It is because of this fact that the differences between the normal and abnormal arch are masked when simple linear measurements of the foot in the long axis are taken.

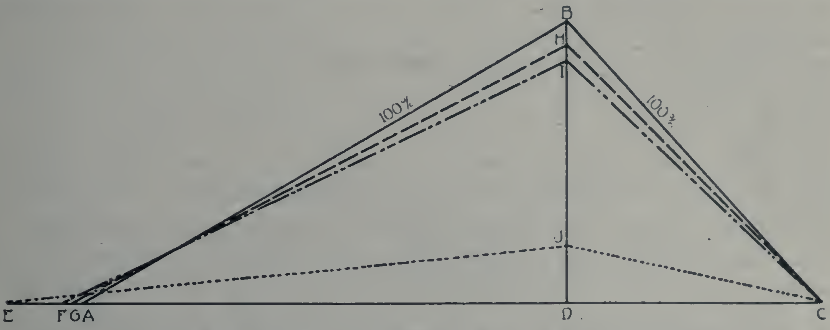


FIG. 7.—Diagram of the depression of arch height in per cent of the original arch height when the foot is subjected to body weight; (*BH*) depression of the arch height of the hypertrophied foot; (*BI*) depression of the arch height of the normal foot; and (*BJ*) depression of the arch height of the moderately pathologic flat foot.

The depression of the arch height of normal and moderately pathologic flat feet under additional loads (Table 20) was calculated in the same manner as previously described. It was from these data that the heel arch length was determined to be a constant. In securing the data it was extremely difficult to project a perpendicular line from the tuberosity of the navicular bone upon the footprint and, therefore, there was considerable experimental error in the determination of the heel arch length. The average heel arch length was obtained, however, for the resting foot, for the arch subjected to body weight, and for the foot when the individual had an added weight upon his back. The average heel arch length was 4.57 centimeters for the resting arch, 4.52 with the body weight, 4.52 with the body weight plus an additional

32 pounds and 4.55 with the body weight plus an additional 64 pounds. Obviously, it would be quite impossible for the heel arch length to become less with the weight of the body upon the foot than it was in the resting foot. The average of these measurements was 4.54 cm. which was taken, therefore, as an approximate constant and was used in the computation of the arch heights of all the various groups.

In the calculation of the depression of the arch due to the various additional loads placed upon it, the hypotenuse of the right triangle, viz., the line from the tuberosity of the scaphoid to the head of the first metatarsal was considered as a constant since this distance did not change when the arch heights under increasing loads were calculated.

The absolute and the percentage depressions of the normal foot and moderately pathologic flat foot will next be considered. Only one individual of the 30 college students had broken arches. The arches in his case approached more nearly the normal than any other case in the pathologic group, although there had been mild symptoms of arch trouble for nearly a year. The percentage depression of the arch height under the body weight in his case was 15, which approximates the average normal depression, and the per cent of depression of the arch height (Table 20, *b*), caused by the addition of 32 and 64 pounds respectively, is proportionally the same as in the normal foot. The percentage decrease of the broken arch, however, is greater than in the normal arch when increasing loads are placed upon the foot. Under an added load of 32 pounds the broken arch decreased 6.5 per cent of its original height, the normal arch only 4.5 per cent, and under an additional load of 64 pounds the broken arch descended to 13 per cent, while the normal arch fell to about 9 per cent.

The depression of the arch height, therefore, is directly proportional to the load put upon the arch both for the normal and the moderately pathologic flat foot. The absolute and percentage depression of the normal foot is considerably less, however, than that of the moderately flat foot under approximately the same loads.

8. The effect of increasing loads upon the arch height is analogous to other changes in the normal foot when it is subjected to increasing loads. A comparison will be made, therefore, of the average absolute linear and areal determinations and the percentage change of these averages, of the absolute increments, of the force, of the distribution of the force, and of the stress upon the normal and the moderately pathologic flat foot when it is subjected to increasing loads.

The average absolute changes in linear and areal determinations of the normal foot and the moderately flat foot when they are subjected to body weight are given in Tables 21, 22 and Figs. 8 and 9.

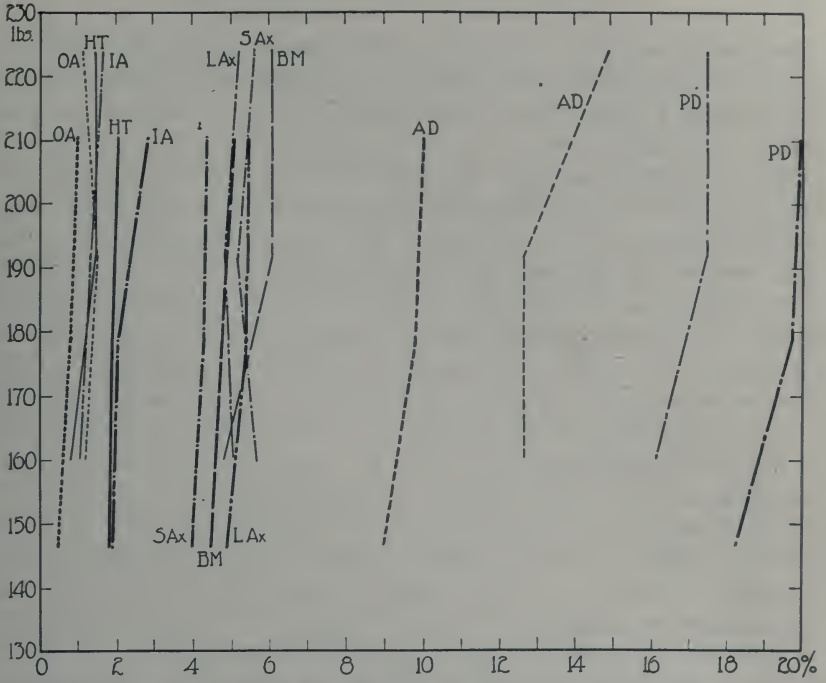


FIG. 8.—The percentage increase in linear determinations of the normal and moderately pathologic flat foot when subjected to increasing loads. The heavy lines represent 58 normal cases; the light, 2 abnormal ones; (*HT*) heel toe; (*OA*) lateral arch; (*IA*) medial arch; (*LAx*) long axis; (*SAx*) short axis; (*BM*) bimetatarsal; (*AD*) anterior diameter; and (*PD*) posterior diameter.

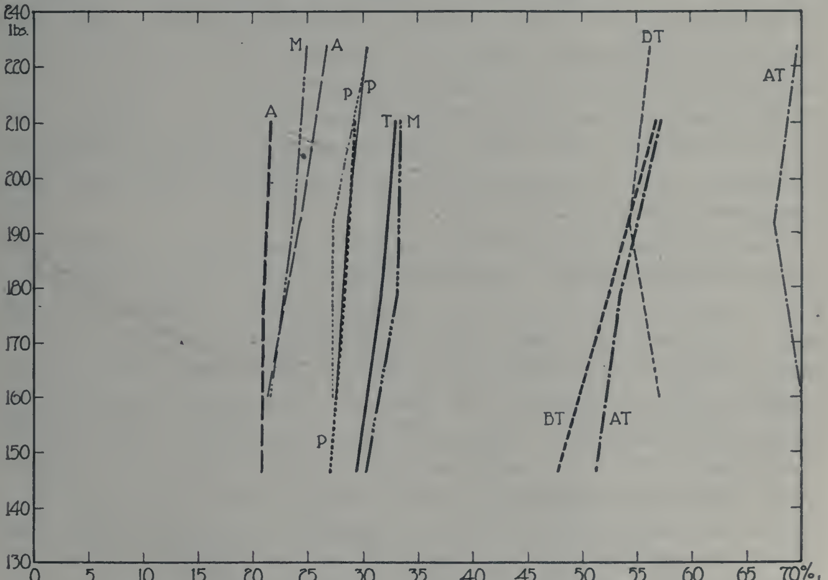


FIG. 9.—The percentage increase in areal determinations of normal and moderately pathologic flat feet when they are subjected to increasing loads. The heavy lines represent 58 normal cases; the light 2 abnormal ones; (*A*) anterior area; (*M*) middle area; (*P*) posterior area; (*BT*) great toe area; and (*AT*) all toes.

The average change in all the linear measurements is quite small and in the more difficult measurements comes within the margin of error. Most of the averages, both linear and areal, show a definite and progressive increase.

The average percentage change of the normal and abnormal foot when subjected to increasing loads, Tables 23 and 24, offer some interesting comparisons. In practically every measurement of the normal foot the per cent increase is in direct proportion to the body weight. The greatest per cent increase in linear measurements for the normal foot is the medial arch length which increases from 1.91 per cent to 2.9 per cent. The outside arch also increases from 0.6 per cent to 1.1 per cent under the influence of the additional load. Whether this increase represents entirely the tissue reaction to the increasing loads or the so-called lateral longitudinal arch has not been determined. The middle area shows the greatest percentage increase (approximately 3.4) when the normal foot is subjected to an additional 64-pound load. The posterior area increases about 2.4 per cent and the anterior area less than 1 per cent. In the moderately pathologic flat foot, also, the increase in the middle area is 3 per cent, but the increase of the posterior area has become 3.4 per cent, and that of the anterior area about 5.5 per cent. This extremely large difference in the percentage of increase in the anterior area of the moderately flat foot as against the anterior area of the normal foot, when the arch is subjected to additional loads, is due to a factor already considered—viz., that increasing weights always raise the stress or the force per square centimeter more markedly in the anterior area than in any other.

The absolute increment in the linear and areal determinations upon the normal foot (Table 25) and upon the moderately flat foot (Table 27) decreases in approximately proportional amounts as additional loads are placed upon the foot.

The force, distribution of force and the stress upon the normal foot and upon the moderately pathologic flat foot are shown in Tables 26 and 28 respectively. The per cent which the force to a given area forms of the total force is approximately the same for the normal and abnormal cases. About 23 per cent of the total force is distributed to the anterior area, and this does not seem to change to any great extent under additional loads. About 60 to 63 per cent of the body weight is distributed to the middle area and about 13 per cent to the posterior area. The actual force in pounds increases rapidly as the additional weights are added. The force on the anterior area, in both the normal and the moderately pathologic flat foot, increases about 12 pounds or one-fifth of the added weight, and on the heel, about 8 pounds or one-seventh of the additional weight.

The stress, or pounds per square centimeter, upon the anterior area, or ball of the foot, is approximately 0.45 in the normal foot as against 0.31 in the abnormal. In the middle and the posterior regions of the foot the stress is considerably greater in the normal than in the abnormal. In the middle area it is about 0.52 in the normal to 0.32 in the pathologic foot, while in the posterior area the difference is 0.43 pound per square centimeter in the normal to 0.36 in the broken arch. These results indicate that loads placed upon the normal arch are distributed, for the greater part, first upon the arch itself, next upon the heel and least upon the ball of the foot, while in the case of the moderately broken arch the greater portion of the additional stress caused by a load upon the back is distributed to the ball of the foot, the heel and the arch obtaining about equal and smaller portions of the added burden.

9. All absolute and percentage averages based upon the data of both the normal and abnormal were first calculated for the right and the left foot separately and then for the two considered together. The average absolute linear and areal determinations of the right and the left foot, both with and without the body weight upon the arch, are indicated in Tables 29, 30, 32 and 33. The percentage change in the linear and areal determinations upon the right and the left foot when the weight of the body was acting upon the arch are shown in Tables 31 and 34. By checking the number of times the right or the left measurements predominated over the other an approximate evaluation of the two sides was obtained. It was found in the consideration of the absolute measurements, with and without the body weight upon the arch, that the left side was greater than the right almost twice as many times. The percentage increases were just reversed, the right being larger in about twice as many cases. The significance of this fact is doubtful. Considerable work has been done in an attempt to establish a predominance of the proportions of one side of the body over the other with practically no success. Hesitation is felt, therefore, in stating that the left foot is larger than the right since the data are too few to be sure upon this point.

10. The differences between the right foot and the left are distinctly minor in character. In each case both the absolute and the per cent determinations on the right and the left foot were averaged together and therefore the number of cases were doubled for each group.

The average absolute linear and areal measurements of the foot for each group are shown in Tables 35 and 36. The absolute determinations of the foot which is not subjected to body weight (Table 35) show that the average age, arch height, body length and body weight are very nearly uniform for all the groups. Of all the linear measurements, the only group which differs considerably from the normal is group VI, consisting of the two feet with rigid arches. In this group the anterior diameter of the foot is 6.5 cm. and the posterior diameter 3.7, as compared to the normal of 8.2 and 4.4 respectively. The absolute areal determinations of the resting foot also closely approximate the normal except the middle area of group VI. In the rigid foot this area is practically half the size of the corresponding normal one, probably due to the disuse atrophy of the plantar muscles while the foot was in a plaster cast.

All the average absolute linear and areal determinations upon the various groups of feet which are subjected to the body weight agree very closely with the normal measurements with the exception of the middle area of the rigid arch. Although this area has increased more than double its original area without the body weight upon the foot, it is still about 20 square cm. below the area of the normal foot.

The percentage changes in the absolute areal and linear determinations when the foot is subjected to body weight are shown in Table 37. By a comparison of the percentage increase under load of all linear and areal determinations of each group with the percentage increase of the measurements of the normal foot under similar loads, an index may be obtained of the reaction of each group. The hypertrophied feet of the soldiers who were measured 24 hours after the completion of a 1,000-mile hike show a smaller percentage increase in every linear and areal measurement over those of the normal foot, except the anterior diameter, which is slightly greater. The increase of the inside arch length is only about one-half that of the normal foot, indicating that the hypertrophied plantar muscles prevent the bony arch from yielding to the extent of the normal arch. The anterior, middle and posterior area of the foot shows an increase of 2 to 3 per cent less than that of a normal foot under similar loads.

The hypertrophied feet of the soldiers measured 72 hours after completion of the 1,000-mile journey show a decided change. Every linear measurement of the foot increased to a greater extent under the body weight than do those of the normal foot. The change in the bi-metatarsal length, for instance, is one-half of one per cent greater in the hypertrophied feet than in the normal; in the anterior diameter, it is practically 4 per cent larger, in the posterior diameter 2 per cent, and in the long axis, about one-half of one per cent. In the areal determinations, likewise, there is a greater per cent of yielding than in the normal foot. The middle area of the hypertrophied foot after a three-day rest yields 9 per cent more than it does in the normal foot. The anterior area is about the same as in the normal. The heel area, however, increases 2 per cent more in the normal foot than it does in the hypertrophied foot after a three-day rest.

These results signify that: First, a hypertrophied foot becomes uniformly more unyielding when it is subjected to a load; second, this resistance of the foot against change is due in a large degree to muscular hypertrophy which keeps both the transverse and the longitudinal arch from yielding; third, that the firmness of these hypertrophied muscles disappears very quickly when they are allowed to rest; and, finally, that the connective tissues of the foot are toughened by long marches, since these tissues obviously do not become softened after two or three days of rest. Muscular hypertrophy, therefore, is followed by a period of extreme laxness of the muscles when the cause of the hypertrophy is removed.

The per cent which the moderately pathologic flat foot increases in its linear and areal determinations when it is subjected to body weight is greater in all instances than in the normal foot. The differences between the pathologic and the normal foot in the decrease of the anterior diameter is especially marked, being 13.6 per cent in the abnormal and 9 per cent in the normal. This is due probably to the fact that the transverse arch is much more weakened in the broken arch than in the normal. The increase of inside arch length is especially marked, being about 2 per cent more in the case of the pathologic flat foot than in the normal. This change, however, is relatively small and could easily be overlooked if it were not magnified by the calculated arch height previously described.

The per cent which the rigid arches increase in the areal and linear determinations when they are subjected to body weight is evidently a complex resulting from long disuse of the muscles and more or less ankylosis due to the six weeks' confinement of the foot in the cast. Obviously the increments in the anterior-posterior lengths are somewhat fixed by the partial ankylosis of the bones of the longitudinal arch. The transverse arch, however, yields even more than in the case of the flat foot. The anterior and middle areas of the foot both increase practically the same as in the normal, while the middle area shows a far higher rate of increase than does the normal or even the pathologic flat foot. But while the increase in the middle area in the moderately pathologic flat foot is due to the weakness of the ligaments under the longitudinal arch and a tremendous percentage depression in the arch height, the calculated arch height of the rigid foot has been shown to be normal. The increase of the middle area in the rigid arch, therefore, is due to the disuse atrophy of the plantar muscles and the consequent extremely small absolute area in the medial part of the foot when it is not subjected to the body weight.

The absolute increments in the linear and areal determinations of the various groups (Table 38) were next calculated. The increase in toe, anterior and posterior area of all the groups is similar to the normal. All the groups except the hypertrophied feet which were measured on the first day show an increase of the middle area slightly greater than the normal.

Calculation of the force, the per cent of the total force and the stress on the anterior, middle and posterior areas of the foot (Table 39) brings out the unsuspected fact that in all groups of cases, the forces upon the arches are distributed in about the same manner regardless of the condition of the arch. The per cent of the total force and the stress in pounds per square centimeter which go to the anterior, middle or posterior areas are practically uniform for the greatly hypertrophied feet, for the weak, yielding arch and for the normal arch. In other words, the condition of the arch does not modify the distribution of the force or the stress upon it. These factors depend only upon the height of the arch and upon the amount of the weight to which the foot is subjected. Only one exception to this rule must be made, viz., that the stress in pounds per square centimeter of the middle area of the rigid arch is greatly increased (Fig. 10). This is due to the fact that, while approximately the same per cent of force goes to the arch of the rigid foot, the plantar muscles have become so atrophied from disuse that they offer a relatively small absolute area upon which the force must be applied.

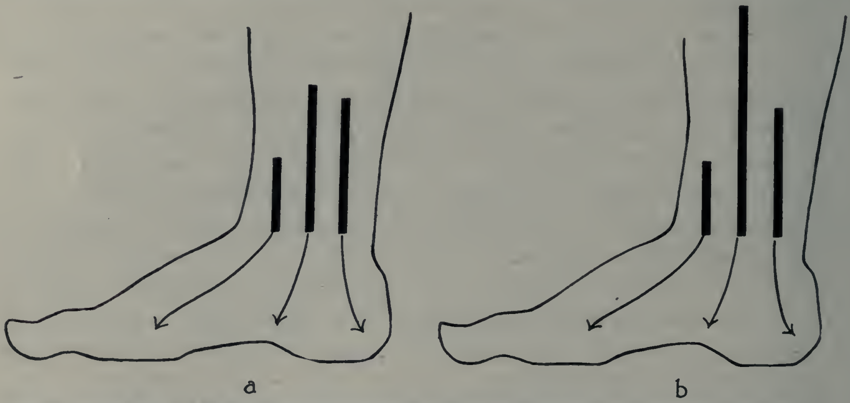


Fig. 10.—Diagrams to show the stress acting upon the anterior, middle and posterior areas of the foot when it is subjected to body weight; (a) foot with normal arch, (b) foot with rigid arch.

11. The distribution of the total body weight to the anterior, middle

and posterior areas of the foot varies with the weight upon the arch and the height of the arch. If the anterior area is studied (Tables 12, 18, 26, 28, and 39), it is obvious that the total force going to this area increases about 5 per cent as the body weight varies from 110 to 160 pounds, or about 1 per cent for every 10 pounds. There is also an increase of approximately 5 per cent in the force which goes to the anterior area as the arch height is increased from 3.7 to 5.1 cm. This indicates that a heavy individual with a high arch sustains a greater per cent of his total body weight upon the anterior part of the foot than would a person of equal weight with a low arch.

A consideration of the forces acting upon the heel indicates that an increase of body weight makes practically no difference upon the distribution of the weight to the posterior area. An increase of the arch height, however, does throw a proportionally greater amount of the body weight upon the heel. Heavier body weights, likewise, make no difference in the weight distribution upon the anterior area although the height of the arch causes a very decided change in the distribution of forces upon this region. The higher the arch the more efficient it becomes mechanically and the more weight it transmits upon the ball and the heel of the foot, sparing the arch from carrying an added burden of the strain. The per cent of the distribution of the force can be summarized briefly by the following table:

	Per cent of force upon ball of the foot	*Per cent of force upon the arch*	*Per cent of force upon the heel*
High arch	Greater	Less	Greater
Heavy body weight	Greater	About the same	About the same

12. The significance of the stresses on the various parts of the foot is somewhat similar to that of the percentage distribution of the body weight upon the arch.

The stress is given in pounds per square centimeter, and represents a true index of the weight distribution for any given area. A summary of the increase of the stresses can be tabulated as follows:

	Ball of the foot	*Arch*	*Heel*
High Arch	4/10 pound / sq. cm.	No increase	3/10 pounds / sq. cm.
Heavy body weight	5/10 pound / sq. cm.	1/10 pound per sq. cm.	1/8 pound / sq. cm

It is interesting to note that, although the high arch throws a smaller per cent of the total force upon the middle area of the foot, it is still subjected to the same amount of stress in pounds per square centimeter. An increase in body weight raises the stresses to a slight degree in both the middle and anterior areas, while the per cents of the forces upon these areas do not change to any extent. From a consideration of these data it is apparent that at least two causative factors must be considered responsible for directing the force of the body weight upon various parts of the foot. The first, and by far the most important one, is the mechanical structure of the arch itself. The higher the arch becomes the more efficiently is it able to transmit the force which it supports. The second and less important factor is the various types of tissue in the foot. The heel reaches its absolute limit of reaction against the weight placed upon it when the foot is subjected to a body weight of about 110 pounds. This must be due to the heavy pad of dense tissue upon the base of the calcaneum which can expand only to a definite limit. The combined rôle which the transverse arch and the tissues of which it is composed play in the reactions of the anterior part of the foot cannot be separated from each other, although in all probability the transverse arch is responsible for the bulk of the reaction against the body weight.

13. Since the longitudinal arch of the foot is largely responsible for distributing the weight of the body to the various parts of the foot, the mechanics of the arch, as indicated by the available data, will be briefly considered.

The longitudinal arch may be considered for explanatory purposes as a simple arch with the astragalus as the keystone, and the calcaneum and the metatarsals as the posterior and the anterior pillars respectively. Instead of the pillars resting against solid bulwarks, as do those of a bridge, for example, they are held in position by ligaments and muscles upon their concave surfaces like a bow held taunt by the bow string. In the resting arch these ligaments and muscles are lax, but when the arch is subjected to the weight of the body they become tense as the ends of the pillars try to separate under the downward force. It is obvious that, as the arch becomes higher, it takes a proportionally smaller force to hold the pillars of the arch together since the mechanical advantage is much greater. Less intrinsic power in the ligaments and the muscles is required, therefore, to sustain a high arch than a low one. Let us assume, for the sake of simplicity, that the ligaments stretch directly between the calcaneum and the head of the first metatarsal bone, as is shown diagramatically in Fig. 11 by the line *AC*. How are the ligaments affected when the arch is subjected to the body weight? Fig. 11 shows a high, low and normal arch drawn to a scale of two. If the high arch *DB* is depressed one centimeter under the body weight, the ligaments are stretched an additional distance of *EA*. If the lowest arch *DI* is depressed the same distance of one centimeter, it would only stretch the ligaments of the foot *GA* or about one-third as much as did the similar decrease of the high arch. It seems clear, therefore, that a depression of a high arch height would strain its supporting ligaments much more than a similar depression of a low one.

On the other hand, as already pointed out, a high arch can be held together by a fraction of the force which is necessary to maintain a low arch. In order to visualize the effects of the various types of arches several sample footprints are included. Fig. 12 (*a*) shows the prints of a normal foot before and after the application of the body weight to the arch. Figs. 12 (*b*), 13 (*a* and *b*) and 14 (*a* and *b*) show examples of prints of moderately pathologic broken arches. The prints of Fig. 13 (*a* and *b*) do not appear flat, although these were both cases showing very marked symptoms. The two cases in Fig. 16 are both normal individuals. The feet represented by Fig. 16 (*b*) were those of a boy about 19 years of age who had never had the slightest symptoms of arch trouble. His weight was 190 pounds and the height of his arch 4.9 cm. In order to support such a heavy body weight upon a relatively short foot, the plantar muscles were greatly hypertrophied. Fig. 16 also represents a foot which is normal in all its reactions to body weight. This individual was a soldier of group II who had marched 1,000 miles without the slightest arch symptoms. Throughout his entire life he had been told that his feet were flat, although they had never given him any trouble. His arch height was extremely low, only 3.5 cm., and yet all the reactions of his foot were perfectly normal. The tuberosity of the navicular bone (shown in the X-ray Fig. 16 (*c*)) does not descend visibly when subjected to body weight. A competent roentgenologist was asked to pass his opinion of these plates, being told that in one case the foot was subjected to body weight and in the

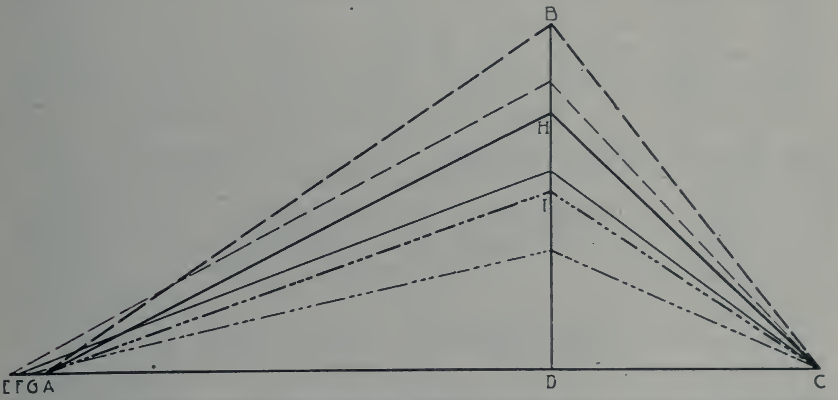


Fig. 11.—Diagram of the effect which the same depression of a high and low arch have upon the medial longitudinal length of the foot.

other it was not. His statement was that "both plates show a second degree flat foot, although the bony deformity does not seem to be changed by weight." The arches appear flat in the X-ray, but they are normal according to functional, symptomatic and physiologic tests.

Other investigators have observed that the low arch is not necessarily a broken arch. Hoffman ('07) stated that impressions are of no value to the diagnosis of arch weakness, and Weed ('12) believed that visual examination would not reveal the potentiality of a given foot. The term of *broken arch* should be used entirely in place of the term *flat foot;* or the use of the expression, *flat foot,* should be reserved for only those cases showing definite symptomatic and physiologic weaknesses of the arch.

Extremely high arches, as illustrated by Fig. 17, give an identically opposite picture. This man was also a soldier who had marched 1,000 miles. He had never had any signs of arch trouble and endured the march without difficulty. The left arch height was 4.5 and the right 5.6. The muscular hypertrophy on the left foot was quite marked, while there was only a thin band of muscle under the right arch. There is no doubt that either the muscle would have hypertrophied if it were necessary in order to sustain the arch, or the arch itself would have broken down under the strain of continued marching. The arch, however, was neither broken nor were the muscles hypertrophied. The height of the arch gave the plantar ligaments a great mechanical advantage, and, consequently, they did not require hypertrophy of the plantar muscles to perform the work required of them.

The mechanism of the arch is undoubtedly more complex than is indicated in this description. Certain facts, however, are outstanding: (1) that a high arch is mechanically more efficient than a low one, (2) that the depression of a high arch causes a much greater relative and absolute increase in the ligaments which support it than does a similar depression in a low arch, and (3) that normally low arches are frequently mistaken for flat feet because of the great amount of muscular development with which they are usually associated.

14. The mechanics of the arch of the foot, as well as the distribution of the force upon the various parts of the foot, has a practical significance in clinical medicine.

The proper appreciation of the high arch is most important from a viewpoint of prevention of a broken arch. The physician often thinks of arch pains as inconsequential if the arch is high and apparently normal. As a matter of fact the high arch breaks down more easily, when the ligaments once start to stretch, than does a low one. Although the high arch offers the greatest mechanical advantage, it also probably

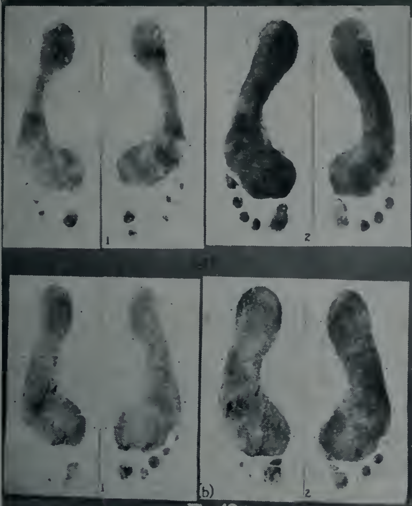


Fig. 12

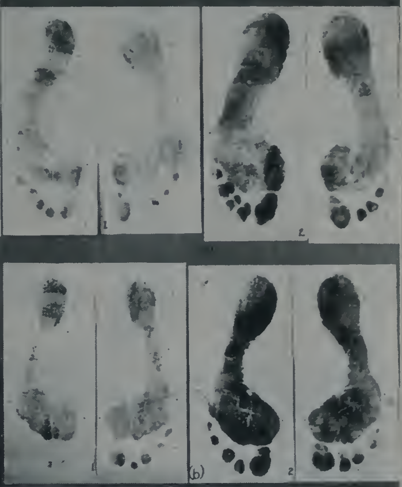


Fig. 13

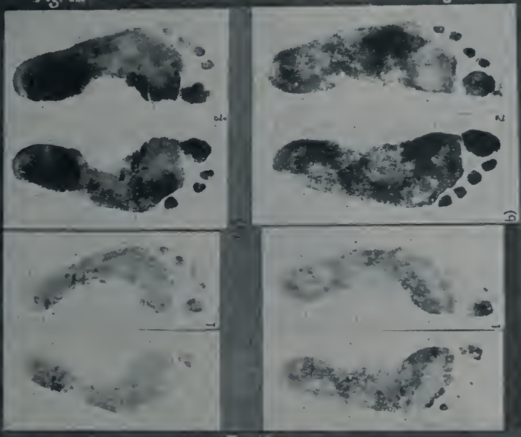


Fig. 14

Fig. 12.—(a) Footprints of normal feet; (1) without body weight; (2) with body weight. (b) Footprints of moderately pathologic flat feet; (1) without body weight, (2) with body weight.

Fig. 13.—(a and b) Footprints of flat feet; (1) without body weight, and (2) with body weight.

Fig. 14.—(a and b) Footprints of flat feet; (1) without body weight, and (2) with body weight.

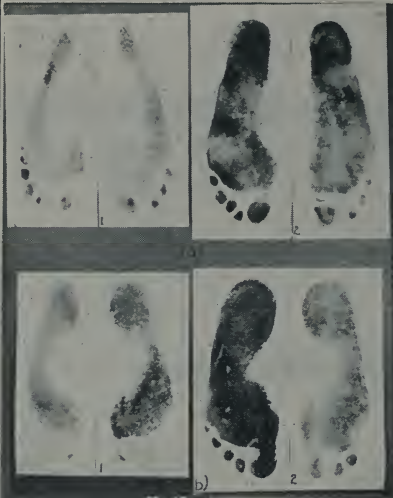


Fig.15

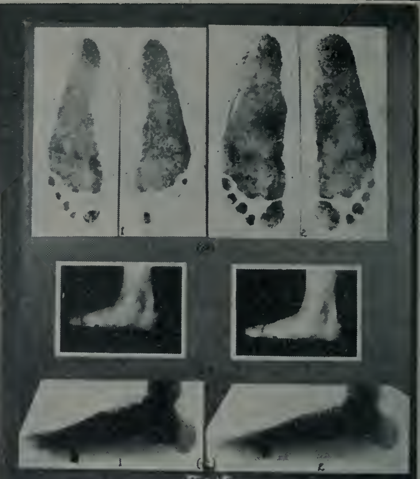


Fig.16

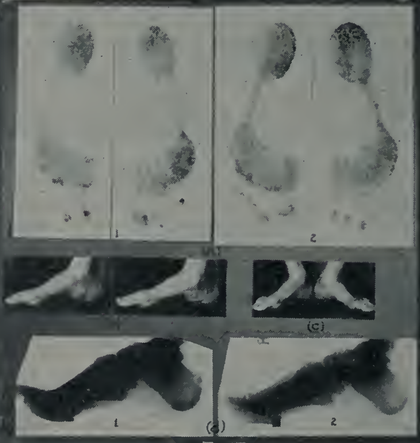


Fig.17

Fig. 15.—(a and b) Footprints of normal feet with low arches; (1) without body weight, and (2) with body weight.

Fig. 16.—(a) Footprints of normal feet with low arch height; (1) without body weight and (2) with body weight.

(b) Pictures of medial view of foot with low arch height; (1) without the body weight and (2) with the body weight.

(c) X-rays of the medial view of normal foot; (1) without the body weight upon the foot, and (2) with the body weight.

Fig. 17.—(a) Footprints of normal feet with extremely high arches, (1) without the body weight, and (2) with the body weight.

(b) Pictures of the right foot with a high arch, (1) without the body weight, and (2) with the body weight.

(c) Pictures of the right and the left foot with and without the body weight upon the arch.

(d) X-rays of the medial view of the right normal foot with a high arch, (1) without the body weight and (2) with the body weight.

has quantitatively less muscle and ligament to support it. Consequently, if the ligaments become weakened from an infection or trauma, there is no reserve muscular power to support the arch. Moreover, a depression of a high arch causes a relatively greater stretching of the ligaments and consequently a greater tension upon them for any given amount of depression. Often the very acute arches are either high or moderately high, since great pain may result from the sudden stretching of the ligaments under the arch. In this case the arch should be tested to see if the ligaments have already been increased in length. If they have not, complete rest should be sufficient in order to restore the foot. If they have already become attenuated, the development of the plantar muscles by exercise should be attempted.

The effect of an additional load upon a moderately flat foot should be remembered, since the increase in the dimensions of the foot are directly proportional to the added weights, and the muscles, therefore, must be accustomed to these additional loads gradually in order to give them time in which to hypertrophy.

The early cases of broken arches can be separated by functional tests from those individuals having acute symptoms but whose plantar ligaments have not yet given under the strain. The greater relative per cent of the medial longitudinal length would suffice to differentiate these in a marked case, but the calculation of the percentage depression of the arch height would be a safer test if the case was a doubtful one. A depression of over 20 per cent should be considered definitely pathological.

The judgment of flat or broken arches by the visual examination by footprints alone, or even by the X-ray, is not sufficient. A functional test under added known weights should be carried out in order to verify the diagnosis.

SUMMARY

1. The relation of the absolute linear and areal determinations to an increase in body weight is not affected by the normality of the arch.

2. The force in pounds upon the anterior, middle or posterior regions of the foot can be calculated by the formula:

$$\text{Unknown force (pounds)} = \left(\frac{\text{Area of the anterior, middle and posterior part of the foot}}{\text{Total calculated area of the foot}}\right) \times \left(\text{Total force on the foot}\right)$$

3. In an individual of light weight the heel is supporting as large a per cent of the body weight as it does in a heavier person.

4. The greater bulk of the additional weight of a heavy individual is thrown upon the anterior part of the foot.

5. No relation was observed between the age in the interval of 16 to 34 years and the absolute linear and areal determinations.

6. The higher the arch, the smaller is the absolute area of the foot needed to support the same amount of the body weight.

7. A high arch throws a greater per cent of the body weight upon the ball and heel of the foot than does a low one.

8. A high arch decreases the per cent of the total force going to the arch crest or apex and thus maintains approximately the same stress upon the middle area of the foot.

9. The range of the calculated arch height in the various groups of cases when the foot is subjected to the body weight is six times as great as the range of the observed resting arch height in the same groups.

10. The arches of the soldiers, who were measured on the first day after ending a 1,000-mile march, were practically unchanged when they were subjected to body weight.

11. The arches of the soldiers, who were measured three days after their 1,000-mile journey, showed as much depression in the arch height as did the normals when subjected to body weight.

12. The broken arch was depressed 80 per cent of its original height when body weight was placed upon it.

13. The ligaments beneath the longitudinal, bony arch not only support it but also limit the amount of depression when the foot is subjected to body weight.

14. Weakened ligaments of the moderately pathologic flat foot permit the arch height to be depressed more than it is in the normal foot.

15. The heel arch length is a constant when the foot is subjected to body weight.

16. The line from the tuberosity of the scaphoid to the head of the first metatarsal is a constant when the foot is subjected to body weight.

17. The depression of the arch height is directly proportional to the load put upon the arch.

18. The absolute measurements upon the left foot seem to be slightly larger in a majority of cases than they are upon the right. No significance is attached to the fact, however, since the variations are small.

19. The average absolute linear measurements of all the various groups agree very closely with the normal determinations.

20. The hypertrophied feet of the soldiers, who were measured the first day after the completion of the 1,000-mile march, show a smaller percentage increase in every linear and areal measurement than do normal feet.

21. The hypertrophied feet of the soldiers, measured 72 hours after their 1,000-mile journey, show that both linear and areal determinations increase to a greater extent than they do in the normal feet.

22. The hypertrophied feet of the soldiers, measured 72 hours after their 1,000-mile journey, become uniformly more yielding when they are subjected to loads.

23. The firmness of the hypertrophied muscles disappears very quickly when the feet are allowed to rest.

24. The subcutaneous tissues of the foot, especially those of the heel, are toughened by long marches and do not become softened by a few days of rest as do the hypertrophied muscles.

25. The per cent of increase of the linear and areal determinations of the pathologic flat foot are uniformly greater than those of the normal foot.

26. The increase in the middle area of the moderately pathologic flat foot is due to the weakness of the ligaments under the longitudinal arch.

27. The large percentage increase in the middle area of the rigid arch is due to the disuse atrophy of the plantar muscles.

28. The percentage distribution of the force and the stress upon the various areas of the foot does not vary to any extent in the different symptomatic groups.

29. The stress on the middle area of the rigid arch is extremely great when the foot is subjected to body weight.

30. The per cent of the distribution of the force in a high arch is greater upon the heel and the ball of the foot and less upon the arch.

31. The per cent of the distribution of the force, when the foot is subjected to a heavy body weight, is greater upon the ball of the foot and about the same on the arch and the heel.

32. The increase of the stress in pounds per square centimeter in a high arch is greater in the heel and the ball of the foot while there is no increase in the middle area.

33. As the body weight becomes heavier, the increase of the stress in pounds per square centimeter is greater on the ball of the foot and less upon the heel and the arch of the foot.

34. Two causal factors are responsible for directing the distribution of the body weight upon the various areas of the foot: (*a*) the mechanical structure of the arch, and (*b*) the types of tissue in the foot.

35. A comparatively small force is necessary to maintain a high arch when it is subjected to the body weight, and thus the mechanical advantage of the high arch is greater than that of the low.

36. Arches frequently appear to be flat and yet may be absolutely normal according to functional and symptomatic tests.

37. A high arch is mechanically more efficient than a low one.

38. The same amount of depression of a high arch causes a much greater absolute and relative increase in the ligaments which support it than does a similar depression of a low arch.

39. Normal low arches are frequently mistaken for flat feet because of the great amount of muscular development with which they are usually associated.

40. A high arch breaks down, when the ligaments are weakened by infection or trauma, more easily than does a low one.

41. The weakened arch can be best differentiated from the normal by determining whether the percentage depression of the original arch height is greater than 20 per cent.

42. A functional test must be applied to flat or broken arches in order to verify the diagnosis.

CONCLUSIONS

Hypertrophied muscles of the foot are relatively unyielding when subjected to body weight.

Hypertrophied muscles of the foot after a few days of rest become weaker functionally than the muscles of a normal foot.

The medial longitudinal arch of the human foot acts mechanically like a true arch in the distribution of additional loads to which it is subjected.

Both the high and the low arch can be functionally normal.

The reaction of an arch to static forces depends almost entirely upon the integrity of the ligaments by which it is supported.

The best criteria of normal and abnormal arches are functional tests.

BIBLIOGRAPHY

(1) Anderson, W. L.: "New methods used in the study of flat foot at Yale." Med. Times, N. Y., vol. 44, May, 1916, 144.

(2) Baisch, B.: "The structure and mechanism of the normal foot and the flat foot." Ztschr. f. orthop. Chir., Bd. xxxi, 1913. Abstract: Am. Jour. Orthop. Surg., vol. 11, 1913, 183.

(3) Belvoe, B.: "Measurement of bones of foot as aid to better diagnosis and more rational treatment." Jour. Missouri State Med. Assn., vol. 14, 1917, 13.

(4) Blodgett, W. E.: "Analysis of one thousand cases of static foot trouble." Am. Jour. Orthop. Surg., vol. 2, 1904, 146.

(5) Bossi, Pietro: "Flat-foot." Monograph. Abstract: Am. Jour. Orthop. Surg., vol. 6, 1908–9, 558. Abstract: Arch. f. orthop. Mech. u. Unfallchir., Bd. 7, 1908, 82.

(6) Bradford and Lovett: "Orthopedic Surgery" (second edition).

(7) Brown, L. T.: "A consideration of the action of the extrinsic and intrinsic muscles of the foot from an anatomical and mechanical standpoint." Am. Journ. Orthop. Surg., vol. 10, 1912, 18.

(8) Codman, C. A. E.: "Diagnosis and treatment of relaxed and weak foot." Pennsylvania Med. Jour., Athens, April, 1911.

(9) Cramer, F.: "Contribution to the subject of flat-foot." Arch. f. orthop. Mech. u. Unfallchir., Bd. 12, 1913, H 12. Abstract: Am. Jour. Orthop. Surg., vol. 11, 1913, 360.

(10) Dane, J.: "Report of some studies upon the arch of the foot in infancy." Jour. Boston Soc. Med. Sc., vol. 3, Feb., 1898, 209.

(11) Elmore, B.: "Report on the flat foot." U. S. Nav. Med. Bull., vol. 7, 1913, 102.

(12) Feiss, H. O.: "A simple method of estimating the common variations and deformities of the foot." Am. Jour. Med. Sc., vol. 139, 1909, 213.

————: "The use of the term 'flat-foot,' with a note on the diagnostic classification of the ordinary disabilities of the adult foot." Boston Med. and Surg. Journ., Oct. 28, 1909, 624.

————: "Die Messung des Fusses, seiner verschiedenen Formen und Deformitäten," Ztschr. f. orthop. Chir., Bd. 26, 1911, 156. Abstract: Zentralbl. f. chir. u. mech. Orthop., 1911, 122.

(13) Harris, J. R.: "Flat feet—the etiological relation of posture and gaits thereto." MILITARY SURGEON, vol. 34, 1914, 1.

(14) Heiner, R. G.: "Flat foot and its relation to the Navy." U. S. Nav. Med. Bull. vol. 5, 1911, 451.

(15) Hoffmann, P.: "Conclusions drawn from a comparative study of the feet of barefooted and shoe-wearing peoples." Am. Jour. Orthop. Surg., vol. 3, Oct., 1905, 105.

————: "A statistical study of the relation between the height of the longitudinal arch and the function of the foot." Am. Med., vol. 13, Aug., 1907, 467.

(16) Holcomb, R. C.: "Weak foot." U. S. Nav. Med. Bull., vol. 7, July, 1913, 321.

(17) Hubscher: "Atrophy of the flexor longus hallucis in flat-foot." Ztschr. f orthop. Chir., Bd. 17, 1907. Abstract: Am. Jour. Orthop. Surg., vol. 5, 1907, 264.

(18) Jones, A. S.: "Making the feet for military service." MILITARY SURGEON, vol. 41, 1917, 219.

(19) Katzenstein, M.: "Induced hardening of ligaments cures flat foot." Deutsch. med. Wchnschr., Bd. 40, July 23, 1914, 537.

(20) Mebane, T. S.: "The foot problem." MILITARY SURGEON, vol. 43, Oct., 1918, 377.

(21) Merrill, W. J.: "Causes, mechanism, and treatment of flat foot." Surg., Gynec and Obst., vol. 22, 1916, 366.

(22) Muskat: "A new method of taking prints of the foot." Ztschr. f. ärztl. Fortbild., 1909, 3. Abstract: Am. Jour. Orthop. Surg., vol. 7, 1909, 279.

(23) Ogilvy: "Painful affections of the feet." Med. Rec., N. Y., Jan. 21, 1905.

(24) Quenu, E., and Kuss, G.: "A research on the anatomy and physiology of the foot." Abstract: Am. Jour. Orthop. Surg., vol. 8, May, 1911, 754.

(25) Richardson, G. H.: "The disabled foot in the military service and its diagnosis by the use of the skiagraph." MILITARY SURGEON, vol. 23, 1908, 107.

(26) Rogers, J. F.: "The leverage of the foot." Anat. Rec., vol. 16, 1919, 317.

(27) Schüman: "Zur Methodik der Plattfussdiagnose." München. med. Wchnschr., Jan. 9, 1906, 81.

(28) Selter: "Flat-foot in child." Jahrb. f. Kinderh., N. F., vol. 57, 1900, H. 6. Abstract: Am. Jour. Orthop. Surg., vol. 2, 1904, 309.

(29) Smith, E. H.: "Arch defects of the human foot." Calif. State Jour. Med. vol. 16, 1918, 256.

(30) Spitzy, H.: "Pes planus." Ztschr. f. orthop. Chir., 12, 1904, H. 4. Abstract: Am. Jour. Orthop. Surg., vol. 2, 1904, 120.

(31) Tubby, A. H.: "The structure and functions of the foot." Jour. Roy. Army Med. Corps., vol. 19, 1912. Also, U. S. Nav. Med. Bull., vol. 6, 1912, 608.

————: "Deformities including diseases of the bones and joints" (second edition), vol. 1. London, 1912.

(32) United States. "Defects found in drafted men." War Department. (Compiled from the draft records.) 1920.

————: "Statistics—The medical department of the United States Army in the World War." Vol. 15, Part I, Army Anthropology, 1921.

(33) Walsham, W. J., and Hughes, W. K.: "Deformities of the human foot." New York, 1895.

(34) Weed, F. W.: "A study of the foot and foot wear." MILITARY SURGEON, vol. 30, 1912, 170.

(35) Weidenreich, Franz: "Der Menschenfuss." Stuttgart, 1921, 254.

(36) Whitman, R.: "Orthopedic Surgery" (sixth edition), 1920.

————: "A study of the weak foot." Tr. Am. Orthop. Assn., vol. 8.

————: "Observations on seventy-five cases of flat-foot." Tr. Am. Orthop. Assn., vol. 1, 1903.

(37) Williams, A. H.: "Static foot error in private practice." Am. Jour. Orthop. Surg., vol. 7, 1909, 481.

TABLE 1.—THE RELATION BETWEEN BODY WEIGHT AND THE LINEAR AND AREAL DETERMINATIONS UPON THE FOOT WHEN NOT SUBJECTED TO BODY WEIGHT.
(Group I.)

Range of body weight (lbs.)	No. of cases	Average body weight (lbs.)	Medial longitudinal length (cm.)	No. of cases	Average body weight (lbs.)	Linear measurements (cm.)							Areal determinations (sq. cm.)					
						Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	......	....	....	2	110	8.5	7.2	3.7	16.4	15.3	11.3	10.4	3.5	5.6	20.9	28.4	6.0	60.9
120–130	2	127.0	12.0	4	126	9.5	8.2	4.5	19.7	17.9	13.5	11.7	3.7	6.6	26.0	48.9	10.6	92.0
130–140	10	134.2	12.6	26	133	9.3	7.9	4.1	19.4	17.8	13.0	12.1	3.2	5.9	26.1	38.2	9.7	79.8
140–150	32	144.9	12.8	44	144	9.7	8.1	4.4	19.8	18.2	13.0	12.1	4.3	7.7	28.4	41.4	11.0	88.1
150–160	16	154.2	13.3	28	153	10.1	8.6	4.5	20.6	18.5	13.2	12.1	4.1	7.8	30.5	46.5	12.1	95.9
160–170	12	163.7	12.9	22	163	9.7	8.3	4.4	20.0	18.5	13.0	12.5	4.5	8.0	27.9	45.0	11.3	92.1
170–180	9	174.0	13.7	11	173	10.0	8.4	4.8	21.2	19.2	13.8	12.3	4.7	8.5	31.2	44.5	14.8	99.0
180–190	0	....	....	0	......	......	......	......	......	......	......	......	......	......	......	......	......	......
190–200	0	....	....	2	192	10.0	7.8	5.0	18.8	16.3	12.7	11.8	1.5	1.5	21.1	51.8	11.2	85.6

TABLE 2.—THE RELATION BETWEEN BODY WEIGHT AND THE AREAL DETERMINATIONS OF THE FOOT WHEN SUBJECTED TO BODY WEIGHT. (GROUP I)

Range of body weight (lbs.)	No. of cases	Average body weight	Areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	2	110	5.7	11.3	25.8	45.8	9.6	92.4
120–130	4	126	7.5	12.5	30.2	72.2	14.8	129.4
130–140	26	133	6.5	12.1	32.0	59.0	14.1	117.4
140–150	44	144	7.2	12.8	33.7	61.8	15.0	123.4
150–160	28	153	7.1	13.0	35.4	65.6	16.7	131.0
160–170	22	163	8.4	14.4	34.4	66.3	16.4	131.6
170–180	11	173	7.9	13.8	37.9	68.8	19.4	139.8
180–190	......	......	......	......	......	......	......	......
190–200	2	192	8.4	13.5	33.6	79.5	18.5	145.6

TABLE 3.—THE RELATION BETWEEN BODY WEIGHT AND THE LINEAR AND AREAL DETERMINATIONS OF THE FOOT WHEN NOT SUBJECTED TO BODY WEIGHT

(Groups II and III.)

Range of body weight (lbs.)	No. of cases	Average body weight (lbs.)	Medial longitudinal length (cm.)	No. of cases	Average body weight (lbs.)	Linear measurements (cm.)							Areal determinations (sq. cm.)					
						Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	2	119	11.2	2	119	9.6	7.2	3.5	18.2	16.9	11.3	10.5	3.2	7.1	32.4	19.6	9.8	68.7
120–130	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......
130–140	12	137	12.4	12	137	9.5	7.6	3.8	19.2	17.5	12.6	11.3	2.9	5.5	28.6	37.6	9.8	81.4
140–150	12	143	13.1	12	143	9.9	8.0	4.2	20.3	18.6	13.0	11.8	3.8	6.6	31.5	38.6	12.9	89.8
150–160	6	154	12.9	6	154	9.6	7.3	4.3	20.1	18.7	12.8	12.1	3.7	6.2	30.6	31.3	11.9	79.9
160–170	4	162	12.6	4	162	10.2	8.4	4.9	20.6	19.4	12.6	12.3	3.2	6.7	35.1	39.9	16.2	97.9
170–180	2	174	13.2	2	174	11.0	8.5	5.0	22.1	20.5	13.3	12.6	5.0	9.7	36.4	51.0	20.1	117.1
180–190	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......
190–200	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......

TABLE 4.—THE RELATION BETWEEN BODY WEIGHT AND THE AREAL DETERMINATIONS OF THE FOOT WHEN SUBJECTED TO BODY WEIGHT. (GROUPS II AND III.)

Range of body weight (lbs.)	No. of cases	Average body weight	Areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	2	118	6.2	11.1	37.2	45.2	15.2	108.7
120–130	......	......	......	......	......	......	......	......
130–140	12	137	6.1	9.2	33.5	60.3	14.9	117.7
140–150	12	143	6.8	10.6	38.0	63.5	17.5	129.6
150–160	6	154	6.0	9.6	36.9	48.5	15.7	110.7
160–170	4	162	7.0	11.2	40.0	58.2	19.8	129.3
170–180	2	174	7.4	14.6	42.8	63.0	23.9	144.2
180–190	......	......	......	......	......	......	......	......
190–200	......	......	......	......	......	......	......	......

TABLE 5.—THE RELATION BETWEEN BODY WEIGHT AND THE LINEAR AND AREAL MEASUREMENTS OF THE FOOT WHEN NOT SUBJECTED TO BODY WEIGHT.

(Groups I, II, and III.)

Range of body weight (lbs.)	No. of cases	Average body weight (lbs.)	Medial longitudinal length (cm.)	No. of cases	Average body weight (lbs.)	Linear measurements (cm.)							Areal determinations (sq. cm.)					
						Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	2	119	11.2	4	114	9.0	7.2	3.6	17.3	16.1	11.3	10.4	3.4	6.3	26.6	24.0	7.9	64.8
120–130	2	127	12.0	4	126	9.5	8.2	4.5	19.7	17.9	13.5	11.7	3.7	6.6	26.0	48.9	10.6	92.0
130–140	22	136	12.5	38	134	9.4	7.8	4.0	19.4	17.7	12.8	11.9	3.1	5.8	26.9	38.0	9.7	80.4
140–150	44	145	12.9	56	144	9.8	8.1	4.3	19.8	18.3	13.0	12.1	4.2	7.5	29.1	40.8	11.4	88.5
150–160	22	154	13.2	34	154	10.0	8.3	4.5	20.3	18.6	13.2	12.1	4.0	7.5	30.5	43.6	12.1	93.1
160–170	16	163	12.8	26	163	9.8	8.3	4.5	20.1	18.6	12.9	12.5	4.3	7.8	29.0	44.2	12.1	93.0
170–180	11	174	13.7	13	173	10.2	8.4	4.8	21.3	19.4	13.8	12.3	4.7	8.7	32.0	45.6	15.5	101.8
180–190	......	....	....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
190–200	......	....	....	2	192	10.0	7.8	5.0	18.8	16.3	12.7	11.8	1.5	1.5	21.1	51.8	11.2	85.6

TABLE 6.—THE RELATION BETWEEN BODY WEIGHT AND THE AREAL DETERMINATIONS OF THE FOOT WHEN SUBJECTED TO BODY WEIGHT.
(GROUPS I, II, AND III.)

Range of body weight (lbs.)	No. of cases	Average body weight	Areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	4	114	6.0	11.2	31.5	45.5	12.6	100.6
120–130	4	126	7.5	12.5	30.2	72.2	14.8	129.4
130–140	38	134	6.4	11.2	32.4	59.4	14.4	117.5
140–150	56	144	7.2	12.4	34.6	62.2	15.6	124.7
150–160	34	154	6.9	12.2	35.7	62.6	16.6	127.4
160–170	26	163	8.2	14.0	35.3	65.0	16.9	131.3
170–180	13	173	7.8	13.9	38.6	67.8	20.0	140.4
180–190	.....	.....	.....	.....	.....	.....	.....	.....
190–200	2	192	8.4	13.5	33.6	79.5	18.5	145.6

TABLE 7.—THE RELATION BETWEEN BODY WEIGHT AND THE LINEAR AND AREAL DETERMINATIONS OF THE FOOT WHEN NOT SUBJECTED TO BODY WEIGHT.

(Groups IV, V and VI.)

Range of body weight (lbs.)	No. of cases	Average body weight (lbs.)	Medial longitudinal length (cm.)	No. of cases	Average body weight (lbs.)	Linear measurements (cm.)							Areal determinations (sq. cm.)					
						Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......	......
120–130	2	127	11.4	2	127	8.6	7.1	3.5	17.9	16.5	11.5	11.2	4.6	8.3	26.9	31.1	6.3	72.5
130–140	8	134	12.0	8	134	9.5	7.8	3.7	18.9	17.3	12.0	11.2	3.7	6.7	27.9	35.2	9.8	79.6
140–150	4	147	12.7	4	147	10.0	7.8	4.2	19.1	17.7	12.7	12.1	4.7	8.3	27.4	34.8	9.2	79.6
150–160	12	155	12.9	12	155	9.9	8.4	4.1	20.3	18.8	12.7	12.5	4.5	8.4	22.9	45.9	11.3	96.8
160–170	2	160	11.9	4	160	10.0	7.4	4.3	20.3	18.2	13.2	12.2	3.6	6.9	27.3	47.1	12.6	93.9
170–180	7	173	14.0	7	173	9.9	8.4	4.6	20.6	18.7	13.9	12.3	4.1	7.6	28.1	55.2	13.6	104.5
180–190	2	184	13.1	2	184	9.4	8.1	3.8	19.4	17.5	13.2	12.0	2.0	4.6	23.8	28.9	10.3	67.6
190–200	2	198	13.6	2	198	10.0	8.4	4.7	20.9	19.0	13.7	13.1	2.2	5.7	29.3	48.5	12.1	95.4

TABLE 8.—THE RELATION BETWEEN BODY WEIGHT AND THE AREAL DETERMINATIONS OF THE FOOT WHEN SUBJECTED TO BODY WEIGHT.

(GROUPS IV, V, AND VI.)

Range of body weight (lbs.)	No. of cases	Average body weight	Areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	......	......	......	......	......	......	......	......
120–130	2	127	5.9	10.1	31.3	53.3	12.2	106.9
130–140	8	134	7.3	11.8	33.0	63.3	16.4	124.0
140–150	4	147	8.9	16.0	35.4	69.0	13.8	134.3
150–160	12	155	8.4	13.8	36.5	73.4	18.2	142.0
160–170	4	160	7.8	16.1	33.9	70.0	17.8	137.8
170–180	7	173	7.9	12.2	34.1	83.0	18.0	147.4
180–190	2	184	8.1	14.7	32.5	55.2	15.4	117.7
190–200	2	198	6.5	13.0	34.2	71.3	17.6	136.1

TABLE 9.—THE RELATION BETWEEN BODY WEIGHT AND THE LINEAR AND AREAL DETERMINATIONS OF THE FOOT WHEN NOT SUBJECTED TO BODY WEIGHT

(Groups I, II, III, IV, V and VI)

Range of body weight (lbs.)	No. of cases	Average body weight (lbs.)	Medial longitudinal length (cm.)	No. of cases	Average body weight (lbs.)	Linear measurements (cm.)							Areal determinations (sq. cm.)					
						Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	2	119	11.2	4	114	9.0	7.2	3.6	17.3	16.1	11.3	10.4	3.4	6.3	26.6	24.0	7.9	64.8
120–130	4	127	11.7	6	126	9.2	7.8	4.2	19.2	17.4	12.8	11.6	4.0	7.2	26.2	42.8	9.2	85.5
130–140	30	135	12.4	46	134	9.4	7.8	4.0	19.3	17.6	12.7	11.8	3.2	5.9	27.1	37.5	9.7	80.3
140–150	48	145	12.9	60	144	9.5	8.1	4.3	19.8	18.2	13.0	12.1	4.2	7.5	28.9	40.4	11.3	87.9
150–160	34	154	13.1	46	154	10.0	8.4	4.4	20.3	18.6	13.1	12.2	4.1	7.8	30.7	44.2	11.9	94.1
160–170	20	163	14.3	30	163	9.8	8.2	4.5	20.1	18.6	12.9	12.4	4.2	7.7	28.8	44.6	12.1	93.2
170–180	18	174	13.8	20	173	10.1	8.4	4.8	21.1	19.2	13.8	12.3	4.5	8.3	30.6	48.9	14.9	102.8
180–190	2	184	13.1	2	184	9.4	8.1	3.8	19.4	17.5	13.2	12.0	2.0	4.6	23.8	28.9	10.3	67.6
190–200	2	198	13.6	4	195	9.5	8.1	4.8	19.9	17.6	13.2	12.4	1.9	3.6	25.2	50.1	11.6	90.5

TABLE 10.—THE RELATION BETWEEN BODY WEIGHT AND THE AREAL DETERMINATIONS OF THE FOOT, WHEN SUBJECTED TO BODY WEIGHT

(Groups I, II, III, IV, V, and VI)

Range of body weight (lbs.)	No. of cases	Average body weight	Areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	4	114	6.0	11.2	31.5	45.5	12.6	100.6
120–130	6	126	7.0	11.7	30.4	65.9	13.9	121.9
130–140	46	134	6.6	11.3	32.6	60.0	14.7	118.6
140–150	60	144	7.2	12.6	34.7	62.6	15.4	125.4
150–160	46	154	7.2	12.8	36.0	65.5	17.0	131.2
160–170	30	163	8.1	14.3	35.1	65.7	17.0	132.2
170–180	20	173	7.8	13.3	37.0	73.2	19.4	142.9
180–190	2	184	8.1	14.7	32.5	55.2	15.4	117.7
190–200	4	195	7.4	13.3	34.0	75.4	18.3	140.9

TABLE 11.—THE RELATION BETWEEN BODY WEIGHT AND THE ABSOLUTE INCREMENTS IN THE AREAL DETERMINATIONS OF THE FOOT, WHEN SUBJECTED TO BODY WEIGHT

(Groups I, II, III, IV, V and VI)

Range of body weight (lbs.)	No. of cases	Average body weight	Differences between areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
110–120	21	114	2.6	5.0	4.9	21.5	4.8	35.8
120–130	6	126	3.0	4.6	4.2	23.0	4.8	36.4
130–140	46	134	3.4	5.4	5.5	22.5	5.0	38.4
140–150	60	144	3.0	5.0	5.8	22.2	4.2	37.5
150–160	46	154	3.1	5.0	5.3	21.3	5.1	37.1
160–170	30	163	3.9	6.6	6.4	21.1	4.9	39.0
170–180	20	173	3.3	5.0	6.4	24.2	4.4	40.1
180–190	2	184	6.2	10.2	8.7	26.2	5.0	50.2
190–200	1	195	5.6	9.7	8.8	25.3	6.7	50.4

TABLE 12.—THE RELATION BETWEEN BODY WEIGHT AND THE FORCE, THE DISTRIBUTION OF FORCE, AND THE STRESS ON THE FOOT WHEN SUBJECTED TO BODY WEIGHT

Range of body weight (lbs.)	Average weight causing increment	No. of cases	Anterior area			Middle area			Posterior area			Total calc. area increment, sq. cm.
			Force (lbs.)	Per cent of total force	Stress pounds sq. cm.	Force (lbs.)	Per cent of total force	Stress pounds sq. cm.	Force (lbs.)	Per cent of total force	Stress pounds sq. cm.	
110–120	114.3	21	18.0	15.7	0.57	78.9	69.0	1.73	17.4	15.3	1.38	31.2
120–130	126.3	6	16.6	13.1	0.55	91.0	72.0	1.38	18.8	14.9	1.35	32.0
130–140	134.0	46	22.2	16.6	0.68	91.6	68.3	1.52	20.2	15.1	1.38	32.9
140–150	144.4	60	25.8	17.9	0.74	99.8	69.1	1.59	18.8	13.0	1.21	32.2
150–160	153.8	46	25.7	16.7	0.71	103.3	67.2	1.58	24.8	16.1	1.46	31.6
160–170	162.8	30	32.0	19.6	0.91	106.4	65.3	1.62	24.5	15.0	1.44	32.3
170–180	173.2	20	31.6	18.3	0.85	119.6	69.1	1.64	21.9	12.7	1.13	35.1
180–190	184.0	2	40.0	21.8	1.23	120.8	65.6	2.19	23.2	12.6	1.51	40.0
190-200	195.0	4	42.1	21.6	1.24	121.0	62.0	1.60	31.9	16.4	1.74	40.7

TABLE 13.—THE RELATION BETWEEN AGE AND THE LINEAR AND AREAL DETERMINATIONS OF THE NORMAL FOOT WHEN NOT SUBJECTED TO THE BODY WEIGHT

Range of age (yrs.)	No. of cases	Average body weight (lbs.)	Average age (yrs.)	Linear measurements (cm.)							Areal determinations (sq. cm.)					
				Bimetatarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
16–19	11	144	17.6	9.6	8.1	4.6	19.8	18.4	13.1	12.3	4.2	7.5	27.4	49.4	11.4	95.7
19–22	30	150	19.4	9.8	8.3	4.4	19.8	18.2	13.0	12.2	3.8	7.2	27.6	42.7	11.6	89.0
22–25	16	151	22.8	9.7	8.0	4.1	19.8	18.3	13.2	12.2	3.9	7.0	28.7	41.5	10.4	87.7
25–28	6	156	25.5	9.9	8.4	4.5	20.2	18.3	13.3	12.4	4.9	8.4	29.1	37.8	11.3	84.2
28–31	3	149	29.3	9.9	8.5	4.5	20.1	18.2	13.0	11.9	4.8	7.9	31.4	42.1	11.2	92.6
31-34	3	151	33.0	9.8	8.0	4.1	20.0	18.2	13.2	11.8	4.8	7.8	30.2	35.1	10.5	83.6

TABLE 14.—THE RELATION BETWEEN AGE AND THE INCIDENCE OF FLAT FOOT

Range of age (yrs.)	Number of cases (absolute)				Number of cases (per cent of total)			
	Walsham and Hughes	Blodgett	Whitman	Williams	Walsham and Hughes	Blodgett	Whitman	Williams
0–10	103	....	98	....	9.6	....	9.8	....
0–12	168	....	....	6	15.6	....	....	2.0
10–15	328	....	199	....	30.4	....	19.9	....
15–20	323	....	227	....	30.0	....	22.7	....
10–20	651	....	426	....	60.4	....	42.6	....
12–20	586	166	....	34	54.4	17.0	....	11.5
20–25	98	....	147	....	9.1	....	14.7	....
25–30	67	....	109	....	6.2	....	10.9	....
20–30	165	260	256	75	15.3	26.6	25.6	25.0
Over 30	159	548	220	185	14.8	56.4	22.0	61.5
30–40	68	234	....	59	6.3	24.1	....	19.5
40–50	30	181	....	56	2.8	18.6	....	18.5
50–60	11	96	....	47	1.0	9.9	....	15.6
Over 60	50	37	....	23	4.6	3.8	....	8.0
60–70	....	35	....	14	....	3.6	....	5.0
70–80	....	2	....	9	....	0.2	....	2.9
Total No. of cases	1,078	974	1,000	3,000	....	....	....	....

TABLE 15.—THE RELATION OF THE ARCH HEIGHT TO THE ABSOLUTE AREAL DETERMINATIONS OF THE NORMAL FOOT WHEN SUBJECTED AND WHEN NOT SUBJECTED TO BODY WEIGHT

Range of arch height (cm.)	Average arch height (cm.)	Average body weight pounds	No. of cases	All toes (sq. cm.)		Anterior (sq. cm.)		Middle (sq. cm.)		Posterior (sq. cm.)		Total (sq. cm.)	
				Without body weight	With body weight	Without body weight	With body weight	Without body weight	With body weight	Without body weight	With body weight	Without body weight	With body weight
2.6–3.0	2.8	169	4	8.4	11.6	31.5	36.4	43.3	71.4	14.9	19.2	98.2	138.6
3.0–3.4	3.3	132	1	10.9	11.7	30.0	33.4	48.0	67.3	14.7	20.7	103.6	133.1
3.4–3.8	3.7	138	10	6.7	11.4	27.8	32.9	42.8	64.7	11.8	15.9	89.2	124.9
3.8–4.2	4.0	147	42	7.0	12.5	28.6	34.2	44.1	65.8	11.2	15.8	90.9	128.2
4.2–4.6	4.4	148	29	7.4	13.3	28.7	34.1	41.2	62.5	10.6	15.2	88.0	125.2
4.6–5.0	4.7	150	27	7.3	13.1	27.4	33.3	41.4	60.8	10.8	15.7	86.9	123.0
5.0–5.4	5.1	155	22	8.2	14.6	28.0	34.7	43.2	62.5	11.0	15.6	90.3	127.4
5.4–5.8	5.4	178	2	5.6	16.8	23.1	34.0	37.6	65.7	11.6	18.4	77.9	134.8

TABLE 16.—THE RELATION OF THE ARCH HEIGHT TO THE PERCENTAGE INCREASE IN THE AREAL DETERMINATIONS OF THE NORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Arch height range (cm.)	Average arch height (cm.)	Average body weight (lbs.)	Number of cases	All toes per cent	Anterior per cent	Middle per cent	Posterior per cent	Total per cent
2.6–3.0	2.8	169	4	26.0	13.3	39.3	21.7	29.1
3.0–3.4	3.3	132	1	6.8	10.2	28.7	29.0	22.2
3.4–3.8	3.7	138	10	39.4	15.4	34.2	26.0	28.6
3.8–4.2	4.0	147	42	42.5	15.7	33.7	30.9	29.6
4.2–4.6	4.4	148	29	43.4	15.9	34.8	31.8	30.2
4.6–5.0	4.7	150	27	43.2	17.6	32.1	32.7	29.5
5.0–5.4	5.1	155	22	43.0	19.1	31.2	29.5	29.1
5.4–5.8	5.4	178	2	67.2	32.4	44.6	35.7	41.5

TABLE 17.—THE RELATION OF THE ARCH HEIGHT TO THE ABSOLUTE INCREMENTS IN THE AREAL DETERMINATIONS OF THE NORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Arch height range (cm.)	Average arch height (cm.)	Average body weight (lbs.)	No. of cases	All toes (sq. cm.)	Anterior (sq. cm.)	Middle (sq. cm.)	Posterior (sq. cm.)	Total (sq.cm.)
2.6–3.0	2.8	169	4	3.2	4.9	28.1	4.3	40.4
3.0–3.4	3.3	132	1	0.8	3.4	19.3	6.0	29.5
3.4–3.8	3.7	138	10	4.7	5.1	21.9	4.1	35.7
3.8–4.2	4.0	147	42	5.5	5.6	21.7	4.6	37.3
4.2–4.6	4.4	148	29	5.9	5.4	21.3	4.6	37.2
4.6–5.0	4.7	150	27	5.8	5.9	19.4	4.9	36.1
5.0–5.4	5.1	155	22	6.4	6.7	19.3	4.6	37.1
5.4–5.8	5.4	178	2	11.2	10.9	28.1	6.8	56.9

TABLE 18.—THE RELATION OF ARCH HEIGHT TO THE FORCE, THE DISTRIBUTION OF FORCE, AND THE STRESS ON THE NORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Range	Average arch height (cm.)	Average body weight (lbs.)	No. of cases	Anterior			Middle			Posterior			Calc. total increment in area
				Force (lbs.)	Per cent of total force	Stress pounds sq. cm.	Force (lbs.)	Per cent of total force	Stress pounds sq. cm.	Force (lbs.)	Per cent of total force	Stress pounds sq. cm.	
2.6–3.0	2.8	169	4	22.2	13.1	0.61	127.3	75.3	1.78	19.5	11.5	1.02	37.3
3.0–3.4	3.3	132	1	15.6	11.8	0.47	88.8	67.2	1.32	27.6	20.9	1.33	28.7
3.4–3.8	3.7	138	10	22.6	16.4	0.68	97.2	70.5	1.50	18.2	13.2	1.15	31.1
3.8–4.2	4.0	147	42	25.8	17.6	0.75	99.8	68.0	1.52	21.2	14.4	1.34	31.9
4.2–4.6	4.4	148	29	25.5	17.3	0.75	100.7	68.1	1.61	21.8	14.7	1.43	31.3
4.6–5.0	4.7	150	27	29.3	19.5	0.88	96.4	64.2	1.59	24.4	16.2	1.55	30.2
5.0–5.4	5.1	155	22	33.9	21.9	0.98	97.8	63.1	1.56	23.3	15.0	1.49	30·6
5.4–5 8	5.4	178	2	42.5	23.8	1.25	109.5	61.3	1.67	26.5	14.8	1.44	45.8

TABLE 19.—THE CALCULATED DEPRESSION OF THE ARCH HEIGHT IN THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Group	Body weight (lbs.)	No. of cases	Medial arch length (cm.)		Arch height (cm.)		Depression of arch	
			Without body weight	With body weight	Observed without body weight	Calculated with body weight	Absolute (cm.)	Per cent of original length
I(a)	146	58	13.09	13.43	4.47	3.75	0.72	16.15
I(b)	151	81	13.04	13.34	4.26	3.60	0.66	15.50
I	149	139	13.06	13.35	4.35	3.73	0.62	14.30
II	148	20	12.92	13.10	4.27	3.90	0.37	8.76
III	143	18	12.50	12.80	4.27	3.66	0.61	14.35
IV	154	25	12.88	13.36	4.11	2.94	1.17	28.48
V	159	14	13.04	13.67	4.25	0.83	3.42	80.40
VI	160	2	11.80	12.10	4.00	3.40	0.60	15.03

TABLE 20.—CALCULATED DEPRESSION OF NORMAL AND MODERATELY PATHOLOGIC FLAT ARCHES WHEN SUBJECTED TO ADDITIONAL LOADS

(a)

Weight upon normal arch	No. of cases	Arch height in normal feet		Weight on moderately pathologic flat arch	No. of cases	Arch height in moderately pathologic feet	
		Absolute (cm.)	Depression of resting arch height (per cent)			Absolute (cm.)	Depression of resting arch height (per cent)
11.0	58	4.47	....	11.0	2	3.35	....
146.4	58	3.99	10.78	160.0	2	2.86	14.63
178.4	58	3.81	14.83	192.0	2	2.68	20.15
210.4	58	3.63	18.77	224.0	2	2.48	26.12

(b)

Weight upon normal arch	No. of cases	Arch height in normal feet			No. of cases	Arch height in moderately pathologic feet		
		Absolute (cm.)	Depression (cm.)	Depression (per cent)		Absolute (cm.)	Depression (cm.)	Depression (per cent)
Body weight	58	3.99	....	....	2	2.86	....	....
+32 lbs....	58	3.81	0.181	4.54	2	2.68	0.185	6.47
+64 lbs....	58	3.63	0.357	8.96	2	2.48	0.385	13.46

TABLE 21.—Average Absolute Change in the Linear and Areal Determinations of the Normal Foot when Subjected to Increasing Loads

Weight upon foot (lbs.)	No. of cases	Linear measurements (cm.)								Areal determinations (sq. cm.)					
		Heel toe	Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
11.0	58	26.0	9.6	8.3	4.6	19.8	18.2	13.1	12.2	3.8	7.1	27.3	46.2	11.5	92.1
146.4	58	26.3	10.2	9.1	5.6	20.8	18.9	13.3	12.3	7.8	14.4	34.1	65.7	15.7	129.0
178.4	58	26.4	10.2	9.2	5.7	20.9	19.0	13.4	12.3	8.1	15.2	34.4	68.5	16.1	134.2
210.4	58	26.6	10.3	9.3	5.8	21.1	19.1	13.5	12.4	8.9	16.3	35.2	70.5	16.6	138.8

TABLE 22.—Average Absolute Change in the Linear and Areal Determinations of the Moderately Pathologic Flat Foot when Subjected to Increasing Loads

Weight upon foot (lbs.)	No. of cases	Linear measurements (cm.)								Areal determinations (sq. cm.)					
		Heel toe	Bimeta-tarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
11.0	2	28.4	10.0	8.3	5.0	21.6	19.2	14.6	12.7	4.9	5.8	26.4	74.3	14.1	120.5
160.0	2	28.7	10.5	9.5	5.9	22.8	20.4	14.8	12.9	11.4	19.5	33.6	94.6	19.4	167.0
192.0	2	28.9	10.7	9.5	6.0	22.7	20.3	14.8	12.9	10.4	17.9	34.9	97.5	19.4	169.6
224.0	2	28.9	10.7	9.8	6.0	22.8	20.4	14.9	12.9	11.2	19.2	35.8	99.1	20.3	174.4

TABLE 23.—AVERAGE PERCENTAGE CHANGE IN THE LINEAR AND AREAL DETERMINATIONS OF THE NORMAL FOOT WHEN SUBJECTED TO INCREASING LOADS

Weight upon foot (lbs.)	No. of cases	Linear measurements (cm.)								Areal determinations (sq. cm.)					
		Heel toe	Bimetatarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
146.4	58	1.8	4.5	9.0	18.2	4.9	4.0	1.9	0.6	47.9	51.1	20.9	30.2	27.1	29.5
178.1	58	1.9	4.8	9.8	19.7	5.4	4.3	2.4	0.9	52.4	53.4	21.1	33.1	28.7	31.8
210.4	58	2.1	5.1	10.1	19.9	5.6	4.4	2.9	1.1	56.8	57.1	21.7	33.6	29.4	33.1

TABLE 24.—AVERAGE PERCENTAGE CHANGE IN THE LINEAR AND AREAL DETERMINATIONS OF THE MODERATELY PATHOLOGIC FLAT FOOT WHEN SUBJECTED TO INCREASING LOADS

Weight upon foot (lbs.)	No. of cases	Linear measurements (cm.)								Areal determinations (sq. cm.)					
		Heel toe	Bimetatarsal	Anterior diameter	Posterior diameter	Long axis	Short axis	Medial arch	Lateral arch	Great toe	All toes	Anterior	Middle	Posterior	Total
160	2	0.9	4.9	12.7	16.1	5.1	5.7	1.0	1.2	57.0	70.1	21.4	21.5	27.2	27.9
192	2	1.5	6.1	12.7	17.5	4.8	5.2	1.4	1.6	54.4	67.5	24.4	23.8	27.4	29.0
224	2	1.5	6.1	14.9	17.5	5.3	5.7	1.7	1.2	56.2	69.6	26.9	25.0	30.6	30.8

TABLE 25.—ABSOLUTE INCREMENTS OF THE AREAL DETERMINATIONS OF THE NORMAL FOOT WHEN SUBJECTED TO INCREASING LOADS

Average weight upon foot (lbs.)	Number of cases	Differences between areal determinations (sq. cm.)					
		Great toe	All toes	Anterior	Middle	Posterior	Total
146.4	58	3.96	7.32	6.84	19.55	4.23	36.89
178.4	58	0.34	0.82	0.29	2.75	0.36	5.18
210.4	58	0.73	1.12	0.82	2.03	0.48	4.57

TABLE 26.—THE FORCE, THE DISTRIBUTION OF FORCE AND THE STRESS UPON THE NORMAL FOOT WHEN SUBJECTED TO INCREASING LOADS

Average body weight causing increment in area (lbs.)	Number of cases	Anterior area			Middle area			Posterior area			Calculated total increment in area (sq. cm.)
		Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	
146	58	32.7	22.3	0.96	93.5	63.8	1.42	20.2	13.8	1.29	30.6
32	58	2.7	8.5	....	25.9	80.9	....	3.4	10.6	....	3.4
64	58	10.0	16.5	....	45.4	70.9	....	8.0	12.5	....	6.7
178	58	37.4	21.0	1.09	116.9	65.6	1.71	24.1	13.5	1.50	34.0
210	58	44.8	21.3	1.27	137.1	65.1	1.94	28.6	13.6	1.72	37.4

TABLE 27.—ABSOLUTE INCREMENTS OF THE AREAL DETERMINATIONS OF THE MODERATELY PATHOLOGIC FLAT FOOT WHEN SUBJECTED TO INCREASING LOADS

Average weight upon foot (lbs.)	Number of cases	Differences between areal determinations (sq. cm.)					
		Great toe	All toes	Anterior	Middle	Posterior	Total
160	2	6.51	13.65	7.25	20.35	5.25	46.50
192	2	—0.71	—1.60	1.25	2.85	0.05	2.55
224	2	0.50	1.30	0.95	1.65	0.90	4.80

TABLE 28.—THE FORCE, THE DISTRIBUTION OF FORCE AND THE STRESS UPON THE MODERATELY PATHOLOGIC FLAT FOOT WHEN SUBJECTED TO INCREASING LOADS

Average body weight causing increment in area (lbs.)	Number of cases	Anterior area			Middle area			Posterior area			Calculated total increment in area (sq. cm.)
		Force (lbs.)	Per cent	Stress (lbs. per) sq. cm.)	Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	
160	2	35.3	22.1	1.05	99.1	61.9	1.05	25.6	16.0	1.32	32.9
32	2	9.6	30.1	....	22.0	68.7	....	0.4	1.2	....	4.2
64	2	18.3	28.6	....	37.1	57.9	....	8.6	13.5	....	7.7
192	2	45.0	23.4	1.29	121.1	63.1	1.20	26.0	13.5	1.34	37.0
224	2	53.6	24.0	1.50	136.2	60.8	1.37	34.2	15.3	1.68	40.5

TABLE 29.—AVERAGE ABSOLUTE LINEAR MEASUREMENTS OF THE NORMAL AND ABNORMAL FOOT WHEN NOT SUBJECTED TO BODY WEIGHT (CM.)

Group	No. of cases		Heel-toe length		Medial longitudinal		Bimeta-tarsal		Anterior diameter		Posterior diameter		Long axis		Short axis		Medial arch		Lateral arch	
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
I(*a*)........	29	29	26.0	26.0	......	......	9.8	9.4	8.3	8.3	4.6	4.6	19.8	19.8	18.1	18.2	13.0	13.2	12.1	12.4
I(*b*)........	40	41	......	......	12.9	13.1	9.7	9.7	8.0	8.2	4.1	4.3	19.9	20.0	18.2	18.4	12.9	13.2	12.1	12.1
II..........	10	10	......	......	12.9	12.9	9.8	9.9	7.8	8.1	4.2	4.3	20.2	20.2	18.5	18.6	12.9	13.0	12.0	11.7
III..........	9	9	......	......	12.4	12.6	9.8	9.9	7.4	7.8	4.1	4.2	19.5	19.6	18.1	18.1	12.4	12.6	11.8	11.4
IV..........	13	12	......	......	12.8	13.0	9.7	9.6	8.2	8.2	4.2	4.2	20.1	19.9	18.5	18.4	12.8	13.0	12.4	12.1
V..........	7	7	28.3	28.6	12.8	12.8	9.9	9.8	8.2	7.9	4.1	3.8	19.6	19.5	17.6	17.9	13.0	13.1	11.7	11.9
			(1 case)		(6 cases)															
VI..........	1	1	......	......	12.0	11.8	9.9	10.0	6.3	6.7	3.9	3.5	18.4	19.5	16.8	17.4	11.9	11.7	11.4	11.6

TABLE 30.—AVERAGE ABSOLUTE LINEAR MEASUREMENTS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT (CM.)

Group	No. of cases		Heel-toe length		Medial longitudinal		Bimeta-tarsal		Anterior diameter		Posterior diameter		Long axis		Short axis		Medial arch		Lateral arch	
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
I(*a*).......	29	29	26.5	26.1	......	......	10.2	10.1	9.2	9.1	5.7	5.5	20.8	20.8	18.9	18.9	13.3	13.4	12.2	12.4
I(*b*).......	40	41	......	......	13.1	13.4	10.1	10.1	8.9	9.0	5.4	5.5	20.9	20.9	18.9	19.1	13.2	13.5	12.2	12.1
II..........	10	10	......	......	13.1	13.2	10.2	10.3	8.6	8.9	5.1	5.4	21.1	21.1	19.2	19.3	13.0	13.2	12.1	11.7
III..........	9	9	......	......	12.7	12.7	10.3	10.4	8.6	8.9	5.3	5.4	20.6	20.5	18.9	18.7	12.7	12.9	11.9	11.4
IV..........	13	12	......	......	13.3	13.3	10.2	10.1	9.1	9.2	5.6	5.7	21.3	21.1	19.3	19.3	13.3	13.5	12.4	12.2
V..........	7	7	28.6	28.9	13.5	13.1	10.5	10.4	9.3	9.3	5.6	5.5	20.8	20.8	18.8	18.7	13.7	13.6	11.9	12.0
			(1 case)		(6 cases)															
VI..........	1	1	......	......	12.1	11.9	10.1	10.0	8.1	8.3	5.4	5.5	19.6	20.0	17.4	17.7	12.1	12.1	11.4	11.7

TABLE 31.—AVERAGE PERCENTAGE CHANGE OF THE LINEAR MEASUREMENTS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Group	No. of cases		Heel-toe length		Medial longitudinal		Bimeta-tarsal		Anterior diameter		Posterior diameter		Long axis		Short axis		Medial arch		Lateral arch	
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
I(*a*).......	29	29	2.0	1.7	......	......	4.9	4.1	9.0	9.0	18.7	17.8	5.0	4.7	4.4	3.6	2.0	1.8	0.7	0.4
I(*b*).......	40	41	......	......	2.0	1.8	4.4	3.7	9.5	8.6	23.2	21.8	5.1	4.4	3.9	3.7	2.6	2.1	0.6	0.5
II..........	10	10	......	......	1.5	1.7	3.9	3.8	9.8	9.8	18.3	20.8	4.5	4.4	3.6	3.7	1.3	1.4	0.5	0.5
III..........	9	9	......	......	2 2	2.5	4.8	4.7	13.5	12.3	22.2	23.0	5.4	4.5	3.9	3.2	2.1	2.6	0.1	0.4
IV..........	13	12	......	......	3.2	2.4	4.9	5.0	10.0	10.4	24.6	25.0	6.1	5.1	4.3	4.9	3.7	3.5	0.4	0.6
V..........	7	7	1.0	0.9	3.6	2.9	5.7	4.9	12.0	15.2	26.7	31.2	5.9	6.5	5.9	4.7	4.1	3.8	1.1	0.7
			(1 case)		(6 cases)															
VI..........	1	1	......	......	0.4	0.4	1.5	0.0	22.2	19.3	27.8	36.4	6.1	2.5	3.5	1.7	1.7	3.3	0.0	0.9

TABLE 32.—AVERAGE ABSOLUTE AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN NOT SUBJECTED TO BODY WEIGHT (SQ. CM.)

Group	No. of cases		Age (yrs.)	Arch height (cm.)		Body length (inches)	Body weight (lbs.)	Areal determinations (sq. cm.)											
								Great toe		All toes		Anterior		Middle		Posterior		Total	
	R.	L.		R.	L			R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
I(*a*)........	29	29	19.2	4.5	4.5	68.1	146	3.8	3.9	6.8	7.3	27.3	27.2	45.7	46.6	11.7	11.3	91.6	92.7
I(*b*)........	40	41	23.3	4.3	4.2	67.8	151	4.0	4.4	7.3	7.9	28.4	29.3	40 2	40.0	10.3	11.1	86.3	88.3
II..........	10	10	25.8	4.3	4.2	67.1	148	3.6	4.2	6.9	7.2	31.2	32.4	41.2	42.1	12.0	12.9	91.3	94.6
III..........	9	9	23.7	4.3	4.2	66.6	143	2 9	3.1	5.7	5.7	29.0	31.7	31.3	33.0	11.5	12.8	77.5	82.5
IV..........	13	12	24.1	4.1	4.1	66.8	154	4.2	4.5	8.2	8.0	29.4	29.1	44.2	45.3	11.7	11.0	93.9	93.4
V..........	7	7	24.0	4.3	4.2	67.1	159	3.4	4.1	5.6	6.8	27.3	27.9	44.2	42.2	11.3	9.7	88.4	86.6
VI	1	1	....	4.0	4.0	68.0	160	2.3	2.2	7.5	8.5	25.5	30.8	20.7	19.2	10.6	11.7	64.3	70.2

TABLE 33.—AVERAGE ABSOLUTE AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT (SQ. C.M.)

Group	No. of cases		Age (yrs.)	Arch height (cm.)		Body length (inches)	Body weight (lbs.)	Areal determinations (sq. cm.)											
								Great toe		All toes		Anterior		Middle		Posterior		Total	
	R.	L.		R.	L.			R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
I(*a*)........	29	29	19.2	4.5	4.5	68.1	146	8.2	7.5	14.7	14.1	34.5	33.8	65.6	65.9	16.3	15.1	129.2	129.8
I(*b*)........	40	41	23.3	4.3	4.2	67.8	151	6.9	7.0	12.2	11.9	34.0	33.8	62.0	62.3	15.4	16.1	123.6	124.2
II..........	10	10	25.8	4.3	4.2	67.1	148	7.4	6.4	12.6	10.1	36.8	37.2	60.3	61.8	16.2	17.8	125.9	126.7
III..........	9	9	23.7	4.3	4.2	66.6	143	6.6	5.5	10.1	8.2	36.7	36.4	54.7	56.9	16.0	17.4	117.6	119.0
IV..........	13	12	24.1	4.1	4.1	66.8	154	8.3	7.8	14.0	12.4	34.8	34.3	71.8	73.8	17.2	17.3	137.8	137.1
V..........	7	7	24.0	4.3	4.2	67.1	159	8.0	8.1	13.8	13.4	34.0	34.9	69.5	70.8	16.7	16.0	134.1	135.1
VI..........	1	1	....	4.0	4.0	68.0	160	4.3	4.1	11.2	14.2	32.8	35.8	41.1	50.0	15.8	16.6	100.9	116.6

TABLE 34.—AVERAGE PERCENTAGE CHANGE OF THE AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Group	No. of cases		Age (yrs.)	Arch height (cm.)		Body length (inches)	Body weight (lbs.)	Areal determinations (sq. cm.)											
								Great toe		All toes		Anterior		Middle		Posterior		Total	
	R.	L.		R.	L.			R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
I(*a*)........	29	29	19.2	4.5	4.5	68.1	146	51.4	44.4	53.5	48.7	20.2	21.6	30.8	29.7	28.3	25.8	30.2	28.7
I(*b*)........	40	41	23.3	4.3	4.2	67.8	151	39.9	34.2	39.4	32.7	16.2	13.1	36.0	36.3	33.9	32.6	30.4	29.1
II..........	10	10	25.8	4.3	4.2	67.1	148	51.3	30.5	45.0	27.5	15.2	12.8	31.6	32.3	26.2	28.5	27.4	25.5
III..........	9	9	23.7	4.3	4.2	66.6	143	56.5	41.5	41.5	26.4	21.2	13.1	43.2	42.3	28.9	27.8	34.0	30.6
IV..........	13	12	24.1	4.1	4.1	66.8	154	40.4	41.5	40.7	34.0	15.4	15.2	38.7	37.9	32.5	36.3	32.3	31.9
V..........	7	7	24.0	4.3	4.2	67.1	159	51.2	51.7	52.4	45.3	19.8	20.0	38.6	41.8	33.7	41.9	35.0	36.3
VI..........	1	1	....	4.0	4.0	68.0	160	46.5	46.4	33.1	40.1	22.2	14.0	49.6	61.6	32.9	29.6	36.6	39.8

TABLE 35.—AVERAGE ABSOLUTE LINEAR AND AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN NOT SUPPORTING THE BODY WEIGHT

Group	No. of cases	Aver. age (yrs.)	Aver. arch height (cm.)	Aver. body length (in.)	Aver. body weight (lbs.)	Linear measurements (cm.)								Areal determinations (sq. cm.)					
						Medial longitudinal	Bimetatarsal	Anterior diam.	Posterior diam.	Long axis	Short axis	Medial	Lateral	Big toe	All toes	Anterior	Middle	Posterior	Total
I(*a*).	58	19.2	4.5	68.1	146	....	9.6	8.3	4.6	19.8	18.2	13.1	12.2	3.8	7.1	27.3	46.2	11.5	92.1
I(*b*).	81	23.2	4.3	67.8	151	13.0	9.7	8.1	4.2	20.0	18.3	13.0	12.1	4.2	7.6	28.9	40.0	10.7	87.3
I....	39	21.6	4.4	67.9	149	....	9.6	8.2	4.4	19.9	18.2	13.1	12.2	4.0	7.4	28.2	42.6	11.0	89.3
II....	120	25.8	4.3	67.1	148	12.9	9.8	7.9	4.2	20.2	18.6	12.9	11.8	3.9	7.0	31.8	41.7	12.5	92.3
III....	18	23.7	4.3	66.6	143	12.5	9.8	7.6	4.2	19.5	18.1	12.5	11.6	3.0	5.7	30.3	32.2	12.2	80.0
IV....	25	24.1	4.1	66.9	154	12.9	9.7	8.2	4.2	20.0	18.4	12.9	12.2	4.3	8.1	29.2	44.7	11.4	93.6
V....	14	24.0	4.3	67.1	159	12.8	9.9	8.0	4.0	19.5	17.8	13.0	11.8	3.8	6.2	27.6	43.2	10.5	87.5
VI....	2	......	4.0	68.0	160	11.9	10.0	6.5	3.7	19.0	17.1	11.8	11.5	2.3	8.0	28.2	20.0	11.2	67.3

TABLE 36.—AVERAGE ABSOLUTE LINEAL AND AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Group	No. of cases	Aver. age (yrs.)	Aver. arch height (cm.)	Aver. body length (in.)	Aver. body weight (lbs.)	Linear measurements (cm.)								Areal determinations (sq. cm.)					
						Medial longitudinal	Bimetatarsal	Anterior diam.	Posterior diam.	Long axis	Short axis	Medial	Lateral	Great toe	All toes	Anterior	Middle	Posterior	Total
I(*a*).	58	19	4.5	68	146	....	10.18	9.13	5.59	20.80	18.92	13.43	12.29	7.80	14.39	34.12	65.74	15.72	129.01
I(*b*).	81	23	4.3	68	151	13.24	10.11	8.93	5.44	20.93	18.98	13.34	12.16	6.95	12.13	33.88	62.14	15.76	123.90
I....	139	22	4.4	68	149	....	10.13	9.01	5.50	20.89	18.96	13.35	12.20	7.31	13.07	33.97	63.63	15.74	126.08
II....	20	26	4.3	67	148	13.10	10.24	8.78	5.25	21.14	19.27	13.10	11.89	6.87	11.30	36.95	61.05	17.02	126.32
III....	18	24	4.3	67	143	12.70	10.31	8.74	5.35	20.30	18.79	12.80	11.65	6.05	9.19	36.61	55.80	16.72	118.30
IV....	25	24	4.1	67	154	13.26	10.16	9.11	5.65	21.18	19.30	13.36	12.30	8.03	13.20	34.53	72.48	17.24	137.46
V....	14	24	4.2	67	159	13.30	10.45	9.31	5.56	20.82	18.74	13.67	11.95	8.03	13.63	34.48	70.13	16.37	134.59
VI....	2	......	4.0	68	160	11.95	10.02	8.20	5.45	19.80	17.55	12.10	11.55	4.20	12.70	34.30	45.55	16.20	108.75

TABLE 37.—AVERAGE PERCENTAGE CHANGE OF THE LINEAR AND THE AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Group	No. of cases	Aver. age (yrs.)	Arch height (cm.)	Body length (in.)	Body weight (lbs.)	Linear measurements (per cent)								Areal determinations (per cent)					
						Med. long.	Bimetatarsal	Ant. diam.	Posterior diam.	Long axis	Short axis	Med. arch	Lat. arch	Great toe	All toes	Anterior	Middle	Posterior	Total
I(a).	58	19	4.47	68	146	....	4.47	8.98	18.23	4.89	3.98	1.89	0.57	47.86	51.11	20.91	30.23	27.09	29.45
I(b).	81	23	4.26	68	151	1.87	4.06	9.02	22.47	4.76	3.82	2.33	0.55	37.00	36.00	14.66	36.15	33.22	29.77
I....	139	22	4.35	68	149	....	4.23	9.00	20.69	4.81	3.88	2.15	0.56	41.51	32.30	17.26	33.68	30.68	29.62
II....	20	26	4.27	67	148	1.60	3.89	9.84	19.56	4.46	3.63	1.37	0.50	40.89	36.27	14.01	31.97	27.32	26.44
III....	18	24	4.27	67	143	2.33	4.71	12.89	22.58	4.95	3.55	2.35	0.23	48.99	33.97	17.15	42.77	28.34	32.28
IV....	25	24	4.11	67	154	2.83	4.95	10.15	24.76	5.59	4.59	3.58	0.50	40.95	37.49	15.33	38.32	34.30	32.10
V....	14	24	4.25	67	159	2.91	5.31	13.60	28.93	6.22	5.29	3.96	0.91	51.47	48.83	19.90	40.21	37.78	35.65
VI....	2	......	4.00	68	160	0.42	0.75	20.80	32.10	4.31	2.58	2.48	0.43	46.45	36.60	18.09	55.60	31.23	38.05

TABLE 38.—ABSOLUTE INCREMENTS OF THE AREAL DETERMINATIONS OF THE NORMAL AND ABNORMAL FOOT WHEN SUBJECTED TO BODY WEIGHT

Group	No. of cases	Average weight	Differences between areal determinations (sq. cm.)					
			Great toe	All toes	Anterior	Middle	Posterior	Total
I(a)...........	58	146	4.0	7.3	6.8	19.6	4.2	36.9
I(b)...........	81	151	2.8	4.6	5.0	22.1	5.0	36.6
I.............	139	149	3.3	5.7	5.8	21.0	4.7	36.8
II.............	20	148	3.0	4.3	5.2	19.4	4.6	33.4
III.............	18	143	3.0	3.5	6.3	23.6	4.6	38.3
IV.............	25	154	3.7	5.1	5.3	27.8	5.9	43.8
V.............	14	159	4.3	7.4	6.9	26.9	5.9	47.1
VI.............	2	160	2.0	4.7	6.2	25.6	5.0	41.0

TABLE 39.—The Force, the Distribution of Force and the Stress of the Normal and Abnormal Foot when Subjected to Body Weight

Group	Average body weight causing increment (lbs.)	Number of cases	Anterior area			Middle area			Posterior area			Calculated total area increment (sq. cm.)
			Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	Force (lbs.)	Per cent	Stress (lbs. per sq. cm.)	
I(*a*).	146	58	32.7	22.3	.96	93.5	63.8	1.42	20.2	13.8	1.29	30.6
I(*b*).	151	81	23.6	15.6	.70	103.8	68.7	1.67	23.7	15.7	1.50	32.1
I....	149	139	27.3	18.3	.80	99.6	66.7	1.56	22.3	15.0	1.42	31.5
II....	148	20	26.2	17.7	.71	98.2	66.6	1.61	23.1	15.7	1.36	29.1
III....	143	18	26.0	18.2	.71	97.9	68.6	1.75	18.9	13.2	1.13	34.5
IV....	154	25	21.0	13.7	.61	109.6	71.3	1.51	23.1	15.1	1.34	38.9
V....	159	14	27.6	17.4	.80	107.8	67.9	1.54	23.5	14.8	1.43	39.7
VI....	160	2	26.7	16.7	.78	111.3	69.6	2.44	22.0	13.7	1.36	36.8

A STATISTICAL ANALYSIS OF THE CAUSES OF PALPABLE LYMPH GLANDS IN THE NEW-BORN *

LOUIS DUNN, M.D., AND HALBERT L. DUNN, M.A., M.D.
MINNEAPOLIS

The variation in the number of discernible lymph nodes in the new-born has given rise to divergent views concerning the normal occurrence. The epidermis and subcutaneous tissue of an infant are so thin and soft that a nerve or artery, a bony protuberance or tendon can readily be misinterpreted as an enlarged gland. External factors, such as coryza, infection and fever, influence the relatively unstable system of the new-born and bring about enlarged lymph nodes. Prenatal factors, such as syphilis, must also be considered. The purpose of this study is to analyze, in a carefully controlled group of cases, some of the manifold causes which give rise to the palpable glands of the new-born. We are grateful to the Asbury Hospital, Minneapolis, for cooperation in the collection of material, and we are also indebted to Drs. R. E. Scammon and W. P. Larson for their valuable suggestions.

The results of previous work done upon this subject are somewhat antagonistic. Jensen [1] published a work upon palpation of the occipital and cervical glands of the new-born during the first nine days of life. He comes to the conclusion, after a study of 240 babies, that no pathologic significance can be attached to the frequent discovery of palpable lymph nodes and that the explanation of this condition on the basis of an infection is illogical. Coerper,[2] after a study of 100 new-born infants, concluded that the swelling of the glands must be due entirely to either an infection or a physiologic activity of the lymph system. Baer [3] agrees with Coerper that the palpability of peripheral glands in the new-born signifies nothing pathologic and presupposes, therefore, no preceding sickness. He also arrives at the sensible conclusion that it is extremely difficult to distinguish between normal glands which are just palpable and moderately pathologic enlargements. He advances this explanation as a reason for the variation in the results of different

---

* Contribution from Asbury Hospital, Minneapolis, and Department of Anatomy, University of Minnesota.

[1] Jensen, T.: Hintere Hals- und Nackendrüsen bei Säuglingen in den ersten neun Lebenstagen, Ztschr. f. Kinderh. **14**:176 (March 28) 1916.

[2] Coerper, C.: Ueber die Palpation peripherer Drüsen und deren klinische Bedeutung bei Kindern der ersten zwei Lebensjahre, Monatschr. f. Kinderh. **13**:458 (Oct.) 1915.

[3] Baer, A.: Zur Schwellung der peripheren Lymphdrüsen im Säuglingsalter, Jahrb. f. Kinderh. **56**:814, 1902.

investigators. Reiche,[4] and Grosser and Dessauer [5] find that a large percentage of cubital glands of infants showing signs of congenital syphilis are palpable. Gundobin,[6] in a study of fifty new-born infants, finds no palpable glands in half of his cases, while in the other half the cervical and inguinal glands appear most frequently. Stahr,[7] Dietrich,[8] Vierordt,[9] Hochsinger [10] and Hess [11] offer data bearing on the subject to a less extent. The results of these authors will be considered later in the discussion.

METHODS AND MATERIAL

The conditions for procuring the data were advantageous. The material was collected during the months of November, December and January (1920 and 1921). Considering the fact that respiratory infections start during the early winter in Minneapolis, it is surprising that more nose and throat infections did not occur. Only one case of coryza was noted in the entire series of 102 cases, and this baby was isolated until the rise in temperature and symptoms had abated. The work was carried out in the babies' ward of the Asbury Hospital. The room was kept at an average temperature of about 80 F., and extreme care was observed in aseptic handling of the babies. The infants were palpated in the morning between 8 and 9 o'clock, and the observations were made every two days. The new-born infants were palpated as soon as possible after birth, usually within the first two hours. Since it was not practical to examine the infants every day, some of the data were obtained on the first, third, fifth, seventh, ninth, eleventh and thirteenth days after birth, and the remaining were secured on the first, second, fourth, sixth, eight, tenth and twelfth days.

The babies were weighed between 8 and 10 a. m., and their rectal temperatures taken and recorded at this time. The senior investigator did the palpation for the entire series in order to eliminate differences in judgment. The baby to be examined was unclothed and placed on a table with its head toward the observer. The investigator palpated all lymph glands in two directions, at right angles to each other. First he felt for the mental and cervical glands. After identifying the presence of the cervical glands, deeper pressure was made in a search for the transverse process of the atlas, which can be mistaken for a lymph node in a malnourished infant. Passing the finger still farther posteriorly, the posterior auricular and occipital nodes were sought for in turn. The axillaries were more difficult to examine. To accomplish this the observer grasped the right arm of the baby with his right hand and palpated the right axilla with the middle finger of his left hand. In order to distinguish between an enlarged lymph node and the head of the humerus, he rotated the arm of the infant and outlined the articular surface of the head of the humerus as it glided beneath his finger. The investigator next palpated the epitrochlear and inguinal nodes. In a majority of cases the inguinal nodes were visible as well as palpable, especially if the legs of the infant were extended and slightly separated.

---

[4] Reiche, A.: Ueber den diagnostischen Wert tastbarer Cubitaldrüsen bei Säuglingen, Monatschr. f. Kinderh. **6**:511 (Oct.) 1908; abstr. Jahrb. f. Kinderh. **68**:494, 1908.

[5] Grosser, P., and Dessauer, A.: Ueber die diagnostische Bedeutung fühlbarer Kubitaldrüsen bei Kindern, München. med. Wchnschr. **58**:1130 (May 23) 1911.

[6] Gundobin, A. P.: Die Besonderheiten des Kindesalters, Berlin, 1912, p. 161.

[7] Stahr, H.: Die Zahl und Lage der submaxillaren und submentalen Lymphdrüsen vom topographischen und allgemein anatomischen Standpunkte, Arch. f. Anat. u. Physiol., December, 1898, p. 444.

[8] Dietrich: Die Palpation der Lymphdrüsen, Sitzungsb. d. phys.-med. Soc. zu Erlang. **18**:52 (July) 1886.

[9] Vierordt, H.: Daten und Tabellen für Mediziner, Ed. 3, Jena, 1906.

[10] Hochsinger, C.: Ueber tastbare Cubital- und Seitliche Thoraxlymphdrüsen im Säuglingsalter, Wien. med. Wchnschr. **57**:2114 (Oct.) 1907.

[11] Hess, A. F.: Enlargement of the Epitrochlear and Other Lymph Nodes in Infants, Arch. Pediat. **24**:602 (July) 1907.

The babies examined numbered 102; fifty-two boys and fifty girls. The series represents 102 consecutive deliveries from 1,100 babies born within a period of twelve months in the maternity department of Asbury Hospital. All the infants were Caucasian. One baby died on the first day as a result of birth trauma and instrumental delivery; another was taken out of the hospital on the second day; all the others stayed at least six days. Eleven went home on the seventh day; thirty-one more left on the ninth day, and only eight babies remained in the hospital after the thirteenth day. Any factor which might influence the number of palpable lymph glands was carefully noted. One child had a cold and temperature of 104 F. on the second day; ten were jaundiced; six had infected eyes; eighteen were circumcised; two had vaginal discharge, which, in one instance, proved to be gonorrheal in origin; twenty-five ran a temperature of more than 100 F. at some time during their sojurn in the hospital; four had infected or moist cord stumps; one showed rectal bleeding; and fifteen were premature infants, weighing between 4 and 5 pounds. The mouth, nose and pharynx were examined for discharge but not for redness of the mucous membrane or slight signs of infection.

The data collected as described above are qualitative and not quantitative. The glands were classified into three types: just discernible, distinctly palpable and swollen. The accuracy of such qualitative data, depending largely upon the judgment and sense of touch of the investigator, can, of course, be questioned since they cannot have the mathematical precision of quantitative measurements. Everything possible was done to eliminate the personal equation. The technic was exactly the same in all cases. The investigator used the same finger to palpate similar nodes and held the babies in identical positions. He knew nothing previous to the completion of the collection of data concerning the results of Coerper, Baer and Jensen in order that their conclusions might not warp his judgment.

While the accuracy of the data depends entirely upon the individual judgment and the care observed in their collection, their significance can only be determined by a qualitative statistical study. In this instance the material was reduced to a percentage basis. By means of this an accurate estimate of results was obtained. Tables were constructed of the accessory factors which might influence the enlargement of lymph glands. Others were made to give detailed data concerning the inguinal, occipital and cervical glands. None were made, however, for the axillary, cubital or mental glands, since these nodes were not palpable in any instance in the entire series. They will be considered in the discussion only.

TABLE 1.—AVERAGE TEMPERATURE AND WEIGHT

Time in Days	No. of Cases	Average Temperature, Degrees	No. of Cases	Average Weight, Pounds
1	72	98.33	99	7.306
2	29	99.06	25	6.956
3	69	98.94	66	6.945
4	24	99.07	17	6.672
5	72	98.35	72	6.993
6	26	98.08	26	6.861
7	57	98.22	56	7.071
8	16	98.36	14	7.021
9	41	98.33	42	7.093
10	12	98.12	10	6.937
11	22	98.17	19	7.181
12	2	97.30	2	7.470
13	6	98.17	6	7.542

CONSIDERATION OF TABLES

The average temperatures and weights of the babies are shown in Table 1. This table affords a check on the normality of the new-born infants under observation. The temperature taken by rectum ranged between 98 and 99 F. In only one group was the average temperature above 99 F. and this one represented twenty-four babies, three of whom had a temperature of more than 101 F. According to the normal figures of Vierordt [9] the average temperature is 100 F. at birth and 99.5 F. during the first week of postnatal life. The temperatures of these new-born infants were lower than normal, owing perhaps to the fact that birth temperatures were taken from about fifteen to twenty minutes after birth, and reflect, therefore, the heat loss resulting from the exposure of the baby. The infants were covered very lightly with only one blanket during their sojourn in the hospital which probably accounts for the slightly subnormal body temperatures.

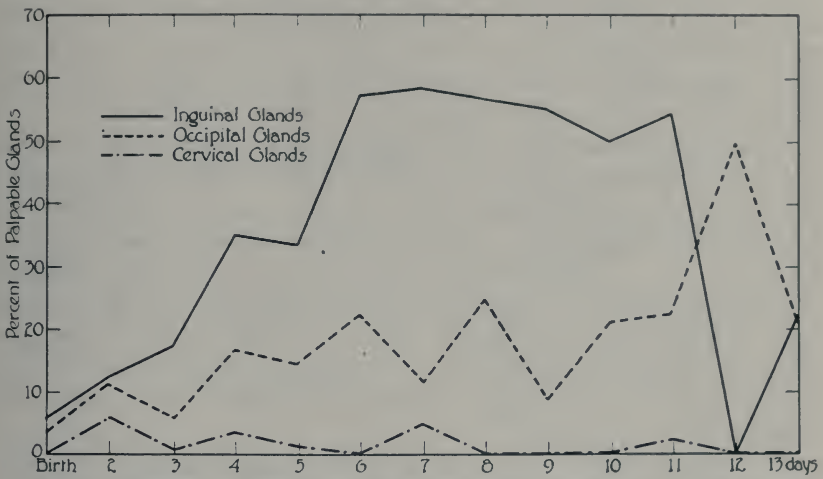


Chart 1.—Degree of palpability of the inguinal, occipital and cervical lymph nodes for each day.

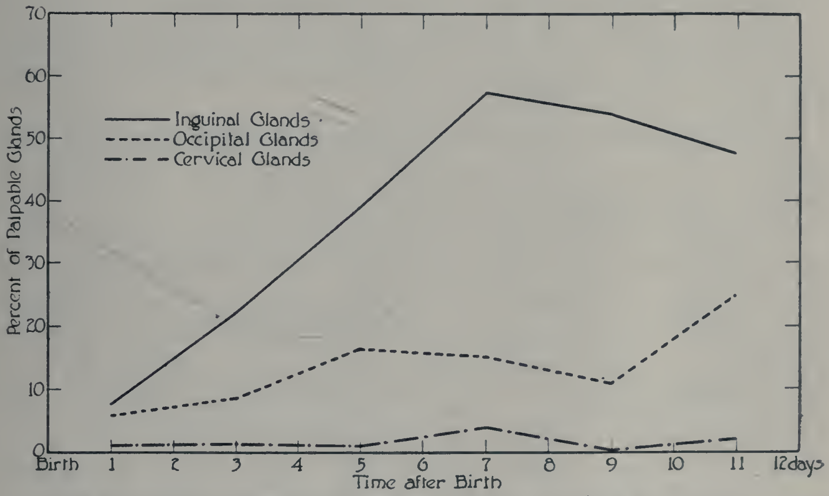


Chart 2.—Degree of palpability of the inguinal, occipital and cervical lymph nodes grouped for each two days.

The average birth weight (Table 1) was 7.3 pounds, which agrees approximately with the average new-born weights given by Emerson and Manny.[12] The postnatal weight loss also agrees with the normal, established by Hammett;[13] this loss amounts to 5 per cent. of the new-born weight on the third day, sinks to 8.6 per cent. on the fourth and then gradually recovers, becoming normal on the twelfth day.

In order to estimate the relative significance of the inguinal, occipital and cervical lymph nodes, the number of palpable glands in the respective regions was counted each day. The percentage of occurrence of palpable lymph nodes was calculated, and the results summarized in Tables 2 and 3. Table 2 shows the percentage presence or absence of these lymph nodes. Owing to insufficient data, the results are somewhat irregular, and consequently Table 3 is prepared from averages based on the same data grouped for two day periods instead of one. A graphic portrayal of the percentage of palpable lymph glands is shown in Charts 1 and 2.

The curve showing the percentage of discernible inguinal nodes (Chart 2) rises steadily from about 8 per cent. on the first day to a height of approximately 58 per cent. on the seventh day and then steadily and gradually falls to 48 per cent. on the eleventh day.

The curve based upon the palpable occipital glands ascends from 6 per cent. on the first day of life to about 16 per cent. on the fifth day, then descends slightly to 11 per cent. on the ninth day, and finally makes a sharp climb to 25 per cent. on the eleventh day.

The curve showing the percentage of cervical involvement shows no definite tendency, the number of cervical glands to be felt on any one day ranging between 0 and 4 per cent.

The percentages of palpable inguinal and occipital glands are correlated with the age of the child in days, while the percentage of swollen cervical glands shows no such correlation.

Other factors besides time influence the percentage of glands which can be palpated. The relation of body weight to discernible lymph nodes (Table 4) demonstrates that the premature infant weighing between 4 and 5 pounds has a very much higher percentage of palpable glands than the child weighing from 5 to 10 pounds. Eighty per cent. of the inguinal glands are enlarged in infants weighing from 4 to 5 pounds in contrast to about 31 per cent. in those weighing from 5 to 10 pounds; 53 per cent. of the occipital and 13 per cent. of the cervical glands in the premature infant are increased in size in contrast to approximately 11 per cent. and 1 per cent., respectively, in the heavier

---

[12] Emerson, W. R. P., and Manny, F. A.: Weight and Height in Relation to Malnutrition, Arch. Pediat. **37**:468 (Aug.) 1920.

[13] Hammett, F. S.: The Relation Between Growth Capacity and Weight at Birth, Am. J. Physiol. **45**:396 (March) 1918.

TABLE 2.—PERCENTAGE PRESENCE AND ABSENCE OF LYMPH GLANDS

Time in Days	No. of Cases	Nonpalpable Lymph Nodes									Palpable Lymph Nodes								
		Inguinal			Occipital			Cervical			Inguinal			Occipital			Cervical		
		Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both
1	102	93.1	95.1	94.1	94.1	98.0	96.1	100.0	100.0	100.0	6.9	4.9	5.9	5.9	2.0	3.9	0.0	0.0	0.0
2	35	85.7	88.6	87.2	85.7	91.4	88.6	94.3	97.1	95.7	14.3	11.4	12.8	14.3	8.6	11.4	5.7	2.9	4.3
3	72	82.0	83.3	82.7	93.0	95.8	94.4	99.6	100.0	99.8	18.0	16.7	17.3	7.0	4.2	5.6	1.4	0.0	0.7
4	27	59.3	70.4	64.9	81.5	85.2	83.4	96.3	96.3	96.3	40.7	29.6	35.1	18.5	14.8	16.6	3.7	3.7	3.7
5	73	64.3	68.5	66.4	83.6	85.0	84.3	97.3	100.0	98.7	35.7	31.5	33.6	16.4	12.3	14.3	2.7	0.0	1.3
6	27	44.4	40.7	42.6	77.8	77.8	77.8	100.0	100.0	100.0	55.6	59.3	57.4	22.2	22.2	22.2	0.0	0.0	0.0
7	67	37.3	46.3	41.8	86.6	89.6	88.1	94.0	95.5	94.8	62.7	53.7	58.2	13.4	10.4	11.9	6.0	4.5	5.2
8	22	40.8	45.5	43.2	72.7	77.4	75.1	100.0	100.0	100.0	59.2	54.5	56.8	27.3	22.7	25.0	0.0	0.0	0.0
9	47	40.4	49.0	44.7	91.5	91.5	91.5	100.0	100.0	100.0	59.6	51.0	55.3	8.5	8.5	8.5	0.0	0.0	0.0
10	12	50.0	50.0	50.0	75.0	83.4	79.2	100.0	100.0	100.0	50.0	50.0	50.0	25.0	16.6	20.8	0.0	0.0	0.0
11	23	43.5	47.9	45.7	82.6	73.9	78.3	95.6	100.0	97.8	56.5	52.1	54.3	17.4	26.1	21.7	4.4	0.0	2.2
12	3	100.0	100.0	100.0	33.3	66.7	50.0	100.0	100.0	100.0	0.0	0.0	0.0	66.7	33.3	50.0	0.0	0.0	0.0
13	7	71.5	85.7	78.6	85.7	71.4	78.6	100.0	100.0	100.0	28.5	14.3	21.4	14.3	28.6	21.4	0.0	0.0	0.0

TABLE 3.—PERCENTAGE PRESENCE AND ABSENCE OF LYMPH GLANDS (GROUPED)

Time in Days	No. of Cases	Nonpalpable Lymph Nodes									Palpable Lymph Nodes								
		Inguinal			Occipital			Cervical			Inguinal			Occipital			Cervical		
		Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both
1- 2	137	91.2	93.4	92.3	91.9	96.3	94.1	98.5	99.3	98.9	8.8	6.6	7.7	8.1	3.7	5.9	1.5	0.7	1.1
3- 4	99	75.8	79.8	77.8	89.9	92.9	91.4	98.0	99.0	98.5	24.2	20.2	22.2	10.1	7.1	8.6	2.0	1.0	1.5
5- 6	100	58.9	62.0	60.5	82.0	85.0	83.5	98.0	100.0	99.0	41.1	38.0	39.5	18.0	15.0	16.5	2.0	0.0	1.0
7- 8	89	38.2	46.1	42.1	83.2	86.6	84.9	95.5	96.6	96.0	61.8	53.9	57.9	16.8	13.4	15.1	4.5	3.4	3.4
9-10	59	42.3	49.2	45.7	88.2	89.8	89.0	100.0	100.0	100.0	57.7	50.8	54.3	11.8	10.2	11.0	0.0	0.0	0.0
11-12	26	50.1	54.1	52.1	76.9	73.1	75.0	96.1	100.0	98.1	49.9	45.9	47.9	23.1	26.9	25.0	3.9	0.0	1.9

TABLE 4.—RELATION OF BODY WEIGHT TO BODY TEMPERATURE AND TO PALPABLE LYMPH GLANDS

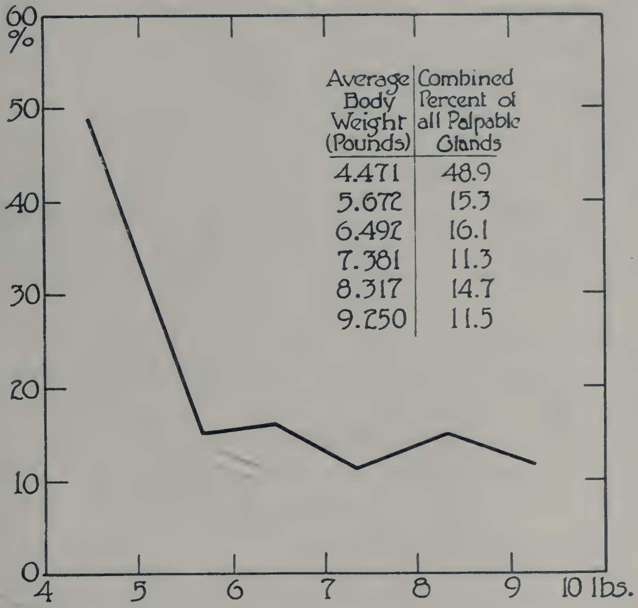
Body Weight, Pounds				Palpable Lymph Glands											
				Inguinal				Occipital				Cervical			
						Average				Average				Average	
Range	Average	No. of Cases	Average Body Temperature, F.	Right Absolute	Left Absolute	Absolute	Per Cent.	Right Absolute	Left Absolute	Absolute	Per Cent.	Right Absolute	Left Absolute	Absolute	Per Cent.
4– 5	4.471	15	98.0	13	11	12.0	80.0	8	8	8.0	53.3	2	2	2.0	13.3
5– 6	5.672	36	98.7	12	9	10.5	29.2	7	5	6.0	16.7	0	0	0.0	0.0
6– 7	6.492	151	98.4	58	51	54.5	36.0	18	14	16.0	10.4	5	1	3.0	2.0
7– 8	7.381	178	98.6	48	48	48.0	26.9	14	8	11.0	6.2	2	1	1.5	0.8
8– 9	8.317	59	98.5	21	17	19.0	32.2	8	5	6.5	11.0	1	0	0.5	0.8
9–10	9.250	13	98.0	3	2	2.5	19.2	2	2	2.0	15.3	0	0	0.0	0.0

TABLE 5.—RELATION OF BODY TEMPERATURE TO PALPABLE LYMPH GLANDS

Body Temperature, F.			Palpable Lymph Glands											
			Inguinal				Occipital				Cervical			
					Average				Average				Average	
Range	Average	No. of Cases	Right Absolute	Left Absolute	Absolute	Per Cent.	Right Absolute	Left Absolute	Absolute	Per Cent.	Right Absolute	Left Absolute	Absolute	Per Cent.
97– 98	97.4	85	32	30	31.0	36.4	14	9	11.5	13.5	0	0	0	0.0
98– 99	98.7	256	102	81	91.5	35.7	33	25	29.0	11.3	9	5	7	2.7
99–100	99.2	78	18	18	18.0	23.1	5	4	4.5	5.8	2	0	1	1.3
100–101	100.3	14	3	3	3.0	21.4	0	0	0.0	0.0	0	0	0	0.0
101–102	101.1	3	0	0	0.0	0.0	1	1	1.0	33.3	0	0	0	0.0
102–103	102.1	3	1	1	1.0	33.3	1	1	1.0	33.3	0	0	0	0.0
103–104	103.3	5	1	1	1.0	20.0	1	0	0.5	10.0	0	0	0	0.0
104–105	104.0	1	1	0	0.5	50.0	1	1	1.0	100.0	1	1	1	100.0

new-born infants. If the percentage of the occipital, cervical and inguinal nodes is averaged (Chart 3), it is seen that 49 per cent. of all glands of the premature infant are palpable. Prematurity, therefore, increases the number of lymph glands which can be palpated in the new-born.

In order to determine whether body temperature is a factor in bringing about an increase in the percentage of palpable lymph glands, the percentage of discernible inguinal, occipital and cervical nodes was determined for each degree of temperature, Fahrenheit (Table 5). With the exception of one infant with a temperature of from 104 to 105 F., who showed a generalized lymphadenopathy, those infants with a normal temperature between 97 and 99 F. showed the highest percentage of lymph node involvement. A temperature of more than 100 F. in the new-born infant, therefore, does not necessarily mean infection with subsequent lymph node enlargement. On the contrary, some other factor than infection must play an important part in the enlargement of the lymph glands.



Average Body Weight (Pounds)	Combined Percent of all Palpable Glands
4.471	48.9
5.672	15.3
6.492	16.1
7.381	11.3
8.317	14.7
9.250	11.5

Chart 3.—Relation of palpability of inguinal, occipital and cervical lymph nodes to body weight.

Other factors which can account for the presence or absence of palpable nodes are considered in Table 6. Sex is the first to be eliminated. There is no difference between male and female. The percentage of inguinal glands enlarged in the male was 72 against 68 in the female, the average involvement being 70. Considering the comparatively few cases involved, no significance can be attached to a 2 per cent. variation above and below the average. The percentage of occipital and cervical glands does not show even minor differences between male and female.

Circumcision was performed on eighteen of the fifty-two boys. The foreskin was consequently somewhat swollen, and it was thought that the operation might account for a small percentage of the inguinal gland enlargement. Consequently, the circumcised boys were separated from the uncircumcised, and it was found that 70 per cent. of the circumcised and 74 per cent. of the uncircumcised (Table 6) showed discernible inguinal glands. This signifies that circumcision plays no part in the production of palpable glands and tends to prove that the lymphatic drainage of the genitalia has no material influence on the high percentage of inguinal nodes noticed in the new-born. To be sure, two girls had vaginal discharges, in one case proved to be gonorrheal in origin, and both had swollen inguinal nodes. The occipital glands of these babies, however, were enlarged also in both instances although they could play no possible part in lymph drainage of the genitalia. The cases were too few, therefore, to conclude that vaginal discharge is a significant factor in the etiology of palpable inguinal nodes.

Six babies had infected eyes. These cases were grouped and show apparently a relationship between the enlargement of occipital glands and eye infections. Eighty-three per cent. of the cases showed a distinct enlargement of the occipital and posterior auricular nodes, while only 21 per cent. without infected eyes had palpable occipital glands. The cases are too few, however, to correlate eye infections as an etiologic factor of occipital gland enlargements.

Temperature has already been discussed as a cause of nodal enlargement, and a glance at Table 6 shows that it plays a decidedly minor rôle. If one considers every temperature of more than 100 F. as abnormal and under 100 F. as normal, normal temperature of the new-born in the first week of life being approximately 99.5 F. according to Vierordt,[9] then rise of temperature shows only a slight correlation to increased lymph node involvement. In the case of inguinal glands, 76 per cent. are enlarged with high temperature and only 68 per cent. with normal. The occipital glands show no difference between high and low temperatures. The cervical glands show a decided variation, 12 per cent. being palpable with high temperatures and only 4 per cent. with normal. This correlation between high temperatures and enlarged cervical glands is probably brought about by mouth and pharyngeal infections which are accompanied by fever. Unfortunately,

TABLE 6.—Causative Factors of Lymphadenopathy

Factors Associated with Lymphadenopathy	No. of Cases	Palpable Inguinal Nodes					Palpable Occipital Nodes					Palpable Cervical Nodes					Axillary Nodes, No.	Epitrochlear Nodes, No.	Mental Nodes, No.
		Right, No.	Left, No.	Both, No.	Average		Right, No.	Left, No.	Both, No.	Average		Right, No.	Left, No.	Both, No.	Average				
					No.	%				No.	%				No.	%			
Males	52	37	38	36	37.5	72	13	13	11	13.0	25.0	4	2	2	3.0	6	0	0	0
Females	50	35	33	32	34.0	68	14	10	10	12.0	24.0	4	2	2	3.0	6	0	0	0
Male and female	102	72	71	68	71.5	70	27	23	21	25.0	24.5	8	4	4	6.0	6	0	0	0
Circumcised	18	13	12	12	12.5	70	8	6	6	7.0	39.0	3	1	1	2.0	11	0	0	0
Uncircumcised	34	24	26	24	25.0	74	5	7	5	6.0	18.0	1	1	1	1.0	3	0	0	0
Cases with vaginal discharge	2	2	2	2	2.0	100	2	2	2	2.0	100.0	0	0	0	0.0	0	0	0	0
Infected eyes	6	5	4	4	4.5	75	6	4	4	5.0	83.0	1	0	0	0.5	8	0	0	0
Uninfected eyes	96	67	67	64	67.0	70	21	19	17	20.0	21.0	7	4	4	5.5	6	0	0	0
Temperature over 100 F. at some time	25	20	18	18	19.0	76	7	5	5	6.0	24.0	4	2	2	3.0	12	0	0	0
Temperature under 100 F. at all times	77	52	53	50	52.5	68	20	18	16	19.0	25.0	4	2	2	3.0	4	0	0	0
With jaundice	10	8	8	8	8.0	80	4	5	3	4.5	45.0	0	0	0	0.0	0	0	0	0
With moist cord stumps	4	2	2	2	2.0	50	1	1	1	1.0	25.0	0	0	0	0.0	0	0	0	0
Rectal bleeding	1	1	1	1	1.0	100	0	0	0	0.0	0.0	1	1	1	1.0	100	0	0	0
With any of the foregoing factors	52	41	39	39	40.0	77	16	14	12	15.0	29.0	6	3	3	4.5	9	0	0	0
With none of the foregoing factors	50	31	32	29	31.5	63	11	9	9	10.0	20.0	2	1	1	1.5	3	0	0	0

all cases of mouth and pharyngeal infections were not discovered, since only purulent discharges from the nose and mouth were recorded.

Icterus neonatorum is also a factor in lymphadenopathy. There were ten cases of jaundice in the 102 babies examined. Eighty per cent. of the jaundiced babies had palpable inguinal nodes, and 45 per cent. had discernible occipital glands. The number of cases is too small to conclude that icterus is a cause of lymph node enlargement.

Another possible factor which might cause enlargement of the inguinal lymph glands is a moist or an infected cord stump. Consequently, the cords were inspected at each palpation. Only four of the 102 babies showed a moist cord stump at some time, and of these four, 50 per cent. had enlarged inguinal glands. If bacterial invasion of the moist cord stumps had taken place, the inguinal lymph nodes which drain the umbilical region would undoubtedly be swollen. The dry cord stumps, however, apparently have a higher correlation with the swollen inguinal glands than do the moist umbilical stumps.

A close inspection of Table 6 shows an apparent difference between the number of glands on the right and left sides of the body. The nodes on the right side of the body apparently predominate over those of the left. The importance of this fact is questionable. The differences are too small and the number of cases are too few to establish the truth beyond question. No significance is attached, therefore, to the apparent difference between the right and left sides.

All the factors, with the exception of an infected throat, which might bring about lymphadenopathy have been considered. The surprising result is that these important factors influence slightly the production of lymph gland enlargement in the new-born. The average inguinal node involvement of male and female (Table 6) is 70 per cent., that of the occipital glands 24.5 per cent. and of the cervical glands 6 per cent. If all cases which are influenced by any accessory factor, such as sex, circumcision, infected eyes, fever and jaundice, are grouped as a unit, 77 per cent. of the inguinal nodes, 29 per cent. of the occipital nodes and 9 per cent. of the cervical nodes are palpable. If all the cases in which none of these factors exist are classed together, only 63 per cent. of the inguinal glands, 20 per cent. of the occipital glands and 3 per cent. of the cervical glands can be felt. This means that the factors mentioned above account for approximately one tenth of the inguinal gland enlargement, one fifth of the occipital nodes and one half of the cervical swellings. It is highly probable that if a close inspection for slight infections of the nasal and pharyngeal cavities had been undertaken all of the palpable cervical glands could be accounted for by known factors. The importance of this detail was not appreciated, however, at the time the data were accumulated.

CAUSES OF LYMPHADENOPATHY

The elimination of external factors which might cause lymph gland enlargement brings us to a consideration of other causes which might produce lymphadenopathy.

Enlarged cervical lymph nodes result from mouth, nasal and pharyngeal infections. This conclusion is supported by Jensen.[1] In a series of 240 new-born infants (Table 7) he found that 10 per cent. showed cervical gland enlargement the first day after birth, 6.6 per cent. on the second day, and the percentage of enlargement steadily diminished to 0.8 per cent. on the seventh day of postnatal life. He believed that mouth and nose infections, usually mild in character, were responsible for these cervical gland enlargements. Coerper[2] agrees with this point of view. He palpated 100 new-born infants (Table 7) and found 34 per cent. of the cervical glands. He believes that infection occurs most frequently in the nasal pharynx, associated with slight catarrh of the first part of the air passages and that the cervical nodes appear with the first sign of infection. The time of year and the amount of coryza may account for the high percentage of palpable cervical glands found in his series.

TABLE 7.—Results of Various Authors in Palpation of the Lymph Glands of the New-Born

		Axillary Nodes		Occipital Nodes		Cervical Nodes		Inguinal Nodes		Cubital Nodes	
Author	No. of Cases	Absolute	Per Cent.	Absolute	Per Cent.	Absolute	Per Cent.	Absolute	Per Cent.	Absolute	Per Cent.
Coerper.....	100	95	95	14	14.0	34	34	17.0	17	2	2
Jensen......	240	..	..	104	43.3	24	10	....	..	..	..
Baer........	25	majority		few	....	few	..	few	..	..	..
Gundoblin..	50	1	2	...	....	..	(Ca) 17	....	(Ca) 17	..	..
Dunn........	102	0	0	25	24.5	6	6	71.5	70	0	0

In respect to the axillary glands there is a wide variation of opinion. Of the 102 babies examined in our series not one axillary gland was palpable. Coerper, however, finds 95 per cent. of the axillary glands present. The five babies which had no discernible axillary nodes were all premature babies of 7 months. He states that the cause for the axillary gland swelling must lie in a process of the tributary field of this gland. But mastitis was found in only two cases and, consequently, the only cause he could assign for the remaining 93 per cent. was the physiologic breast gland swelling of the new-born. Baer[3] also noted the constancy of the axillary node swellings. He palpated the glands of twenty-five new-born infants ranging in age from 10 hours to 5 days and found that the axillary nodes were not only more constant but considerably smaller, while the occipital, cervical and inguinal glands occurred only in isolated cases. Hochsinger[10] and Gundobin[6] believed that Baer palpated small fat lobules in the axilla which he thought to be millet-sized axillary glands. It is our impression also that both Baer and Coerper were deceived as to the presence of lymph glands. The head of the humerus and large nerve trunks as well as fat lobules can readily be mistaken for the axillary nodes. In palpation of these glands in our series the investigator rotated the arm of the baby with one hand while with the fingers of the opposite he searched the axilla. By this means the head of the humerus could be felt gliding beneath the fingers, apparently increasing in size as a larger portion of the articular surface became subcutaneous. The nerve trunks could be differentiated from lymph nodes by palpating in two directions, across them and longitudinally.

Mental lymph nodes were not palpable in a single case in our series and none of the other investigators have made note of them.

Although epitrochlear glands were not found in a single instance in our experiment, several investigators have pointed out their occurrence. Grosser and Dessauer,[5] in a study of 1,066 infants, show that 66 per cent. of congenital syphilitic babies (fifteen in number), 19 per cent. of the rachitic infants (twenty in number) and 4.6 per cent. of the normal children had palpable epitrochlear glands. Hess [11] and Reiche [4] emphasized the value of the epitrochlears as an aid to the diagnosis of congenital syphilis. All three investigators grouped the new-born infants with infants of the first year. In the new-born infant, therefore, the significance of palpable epitrochlear lymph nodes is doubtful.

The occipital and inguinal nodes are still to be considered. The accountable factors which could influence the enlargement of the occipital lymph nodes are infected eyes and jaundice. We know by a consideration of Table 6 that of all the palpable occipital glands approximately 4.5 per cent. are caused by two factors, jaundice and eye infections. Patients with jaundice have 45 per cent. of palpable occipital nodes in contrast to a normal of 24.5 per cent. The six babies with eye infections show 83 per cent. of occipital enlargements. A certain percentage of occipital gland involvement might be accounted for by invasion of the tonsillar crypts by bacteria. Davis [14] and Goslar [15] have shown that bacterial flora invade the tonsils from twenty-four to seventy-two hours after birth and that plasma cells appear in the tonsillar crypts in about two weeks. The sudden increase of enlarged occipital glands from 11 per cent. on the tenth day to 25 per cent. on the thirteenth day is probably a result of tonsillar infection. The accessory factors, jaundice, vaginal discharge and high temperature, account for only 7 per cent. of swollen inguinal glands. The largest portion of occipital and inguinal lymph node involvement occurs as a result of some factor not considered heretofore. Some substance coming from the area drained by these glands must be responsible.

---

[14] Davis, D. J.: On Plasma Cells in the Tonsil, J. Infect. Dis. **10**:142 (March) 1912.

[15] Goslar, A.: Das Verhalten der lymphocytären Zellen in den Gaumenmandeln vor und nach der Geburt, Beitr. z. path. Anat. u. allg. Path. **56**:405, 1913.

What can this factor be? There seem to be four possible causes of inguinal lymph gland enlargement: (1) infection, (2) the sensitization of the new-born infant against the placental foreign tissue as suggested by Abderhalden, (3) a toxic material which might arise from the cord stump, and (4) absorption of a sterile foreign protein by the umbilical lymphatics.

1. Infection is the most common cause of lymphadenopathy. The cardinal signs of local infection are redness, heat, swelling and pain. None are present in the area about the dried stump of the cord. Infection, if severe, usually results in fever, but, as previously shown, the incidence of fever has no correlation with the enlargement of the inguinal nodes. Acute focal infection also gives rise to a leukocytosis in a large majority of cases. In order to see whether the enlargement of the inguinal lymph glands might be correlated with polymorphonuclear leukocytosis, blood counts were taken on fifteen infants about 5 days of age. This work was done by Lippman[16] in connection with a study of the blood of the new-born. Thirteen of the babies had palpable inguinal glands. The normal leukocyte count established by Lippman was 8,000 at birth, about 13,500 at 12 hours, and 3,000 by the fifth day of postnatal life. In all cases the blood count of those infants having palpable inguinal glands agreed with the normal. The curve of inguinal node involvement which rises steadily until the seventh day (Chart 2) is not correlated in any way with the change in the leukocyte count. All cardinal symptoms of infection are lacking in the normal infant, from 5 to 7 days of age, as well as a temperature and leukocytic reaction. Infection is ruled out, therefore, as a possible cause of inguinal lymph gland enlargement.

2. The sensitization of the new-born against the cord proteins is a possible cause of inguinal lymphadenopathy. Abderhalden[17] believed that foreign proteins stimulate the formation of protective substances which are capable of hydrolyzing this protein. These immunizing antibodies are specific and will react only against the inciting substances. If umbilical cord, therefore, is considered to be an antigen, just as Abderhalden believed placental tissue to be foreign protein, antibodies should be developed in the new-born infant against the cord proteins.

To prove the presence or absence of such antibodies, a fresh piece of umbilical cord was secured under sterile conditions. It was ground to very fine pulp and let stand for a week in physiologic sodium chlorid solution containing 0.25 per cent. of tricresol. The extraction was then titrated for one-tenth and one-fifth dilution against sheep's red blood cells and the one-fifth dilution found to be a satisfactory antigen. Samples of blood were taken from five babies (Table 8). They ranged from 3 to 13 days in age and all but one showed palpable inguinal glands. The blood samples were subjected to complement fixation tests which were carried out in a manner similar to that employed in a Wassermann test, except for the use of umbilical cord antigen. In all cases the tests were negative. The enlargement of the inguinal glands, therefore, could hardly be caused by the sensitization of the infant against attached umbilical cord.

---

[16] 16. Lippman, H. S.: Unpublished thesis.

[17] 17. Abderhalden, E.: Weiter Beitrag zur biologischen Feststellung der Schwangerschaft, Ztschr. f. physiol. Chem. **81**:90 (Oct.) 1912.

TABLE 8.—Complement Fixation Blood Reactions and Skin Anaphylactic Tests

Part A.—Fresh Umbilical Cord Used as an Antigen

			Weight, Gm.				Palpable Glands				
							Inguinal		Axillary, Occipital, Cervical		
Case No.	Sex*	Age, Days	At Birth	Present	Temperature	Cord Presence	Right	Left	Right	Left	Blood Reaction
103	♀	3	3,170	2,920	98.4	+	+	—	—	—	—
104	♂	6	4,310	4,260	98.4	+	—	—	—	—	—
105	♀	8	3,025	2,950	98.4	—	+	—	—	—	—
106	♂	8	3,330	3,000	98.2	—	+	—	—	—	—
107	♂	13	3,085	3,070	98.4	—	+	+	—	—	—

Part B.—Umbilical Cord Stumps Used as an Antigen

			Weight, Gm.				Palpable Glands							
							Inguinal		Occipital		Axillary Cervical Mental			
Case No.	Sex*	Age, Days	At Birth	Present	Temperature	Cord Presence	Right	Left	Right	Left	Right	Left	Blood Reaction	Anaphylactic Tests Inspected Daily for Four Days
108	♂	12	4,130	3.910	98.4	—	+	+	—	—	—	—	—	—
109	♀	8	4,055	4,200	98.6	—	+	+	—	—	—	—	—	—
110	♀	10	2,955	2,640	98.6	—	+	+	—	—	—	—	—	—
111	♂	10	3,450	3,480	98.4	—	±	±	—	—	—	—	—	—
112	♂	9	2,840	2,880	98.4	—	—	—	—	—	—	—	—	—
113	♂	10	3,860	3,840	98.4	—	+	+	—	—	—	—	—	—
114	♂	6	3,300	2,980	98.2	—	+	+	+	—	—	—	—	—
115	♀	12	2,063	2,040	98.6	—	+	+	—	—	—	—	—	—
116	♀	8	3,750	3,510	98.4	—	+	+	—	—	—	—	—	—

* In this Column ♀ represents female and ♂, male.

3. The cord stump, however, might contain degenerative products or toxic substances which would cause the inguinal nodes to become swollen. It is known that a toxin can bring about a lymph node enlargement. The effect of diphtheria toxin, for instance, has been studied by several authors. Barbacci[18] and Bulloch and Schmorl[19] come to

---

[18] Barbacci, O.: Ueber die feineren histologischen Alterationen der Milz, der Lymphdrüsen und der Leber bei der Diphtherie-Infection, Zentralbl. f. allg. Path. u. path. Anat. **7**:321 (May) 1896.

[19] Bulloch and Schmorl: Ueber Lymphdrüsenerkrankungen bei epidemischer Diphtherie, Beitr. z. path. Anat. u. allg. Path. **16**:247, 1894.

practically the same conclusion, namely, that lymph glands subjected to diphtheria toxin show a decided hyperemia and a high degree of hyperplasia of the gland parenchyma. Benzancon and Labbe[20] state that in an extreme case of glandular intoxication by diphtheria toxin the picture of necrosis predominates and that only in less severe cases or following the injection of diphtheria antitoxin does active reaction set in. Imamura,[21] studying the effects of tissue reactions of lymph glands to exotoxins, endotoxins and mixed toxins, came to the conclusion that the follicles react against free toxin, necrosis occurring; while against endotoxin, irritation and hyperplasia are the rule.

Since a toxic substance, especially a mildly toxic substance, stimulates a lymph gland to hyperplasia, it was necessary to investigate the cord stumps for such a material. Ten dried stumps were collected as they dropped off. They were macerated and extracted in a physiologic sodium chlorid solution containing 0.25 per cent. of tricresol. The extract was then titrated against sheep's red blood cells, the dilution of one-fifth being selected for the antigen. Blood was taken from nine babies (Table 8). The infants ranged from 6 to 12 days of age, eight of them having palpable inguinal glands. Anaphylactic tests were performed upon the babies using the Pirquet technic, the tuberculin being replaced by a drop of the extract. Complement fixation tests were made upon all the blood specimens, the newly prepared antigen being used. In all cases both blood tests and anaphylactic tests were negative. The enlargement of the inguinal lymph glands, therefore, could not be due to toxic substances in the cord stump.

4. The remaining cause of lymph adenopathy to be considered is the absorption of a sterile foreign protein. Practically no data are available concerning the effect of a sterile protein upon lymph glands. Gilbert and Carnot[22] state that occasionally with eruptions and serum therapy one sees a generalized lymphadenopathy explainable only as a reaction against a foreign protein. Further experimentation along these lines is beyond the scope of this paper. By elimination of infection and toxic causes, we feel justified in stating that, in all probability, the inguinal lymph nodes are enlarged because of the removal of the proteins in the cord stump by way of the lymph stream.

This theory, however, does not explain the enlargement at birth of 4.9 per cent. of inguinal glands and 3.95 per cent. of occipital glands.

---

[20] Benzancon, F., and Labbe, M.: Effets comparés de l'action sur les ganglions du bacille et de la toxine diphtherie, Compt. rend Soc. d. biol. **50**: 507 (May) 1898.

[21] Imamura, H.: Ueber die Gewebsreaktion der Milz und der Lymphdrüsen gegen Toxin, Verhandl. d. Jap. path. gesellsch. Tokyo, 1912, p. 65; abstr. Zentralbl. f. Bakteriol. u. Parasitenk. **60**:680 (March 17) 1914.

[22] Gilbert, A., and Carnot, P.: Bibliothèque de thérapeutique, Paris, 1909. p. 201.

A survey of the thirteen cases (Table 9) in which swollen lymph nodes were palpated at birth shows that only one case of the thirteen was a premature infant, that the average temperature of the group was 98.4 F. and that, in only two instances, did the inguinal and the occipital glands become enlarged simultaneously. A certain percentage of the palpable glands in this group are undoubtedly due to the delay of one to three hours after birth before palpation of the lymph nodes. Lippman[16] has shown that a sudden and marked leukocytosis occurs in the first few hours after birth. Immediate palpation of the newborn infant would eliminate lymph node enlargement which might be due to this leukocytosis. The data of Jensen, which were determined immediately after birth, also show 7.5 per cent. of palpable occipital glands. He connects no pathologic significance to the findings of these glands and expresses his doubt that they have any connection with an hereditary constitutional anomaly. He points out that the glands were present in a case of cesarean section immediately after the extraction of the child and that this disproved the theory of traumatic or infectious origin in the birth canal. A small percentage of infants at birth show enlarged inguinal glands for which the etiology is as yet unknown.

TABLE 9.—Palpable Lymph Glands at Birth

Index No.	Right Occipital	Left Occipital	Right Inguinal	Left Inguinal	Weight Lb.	Weight Oz.	Temperature
9	+	0	0	0	6	5	98.0
41	+	+	+	0	7	1	98.6
64	+	0	0	0	8	5	99.0
75	+	0	0	0	8	5	98.0
79	+	0	0	0	6	6	98.0
86	+	+	+	+	7	9	98.8
21	0	0	+	0	6	15	98.2
29	0	0	+	0	6	6	98.0
39	0	0	+	0	8	10	99.0
67	0	0	+	+	4	5	97.6
76	0	0	0	+	6	15	99.6
77	0	0	0	+	7	2	....
78	0	0	+	+	6	7	97.6
Total	6	2	7	5	(Av.) 7	0	98.4

CONCLUSIONS

1. Daily curves of the percentage of lymph node enlargement show three distinct types: (*a*) the inguinal type which increases steadily from about 8 per cent. on the first day of life to 58 per cent. on the seventh day and then falls gradually to 48 per cent. on the eleventh day; (*b*) the occipital type which increases slightly from 6 per cent. on the first day to about 16 per cent. on the fifth day, descends slightly and then makes a sharp ascent to 25 per cent. from the ninth to the eleventh days, and (*c*) the cervical type which follows no definite course but oscillates between 0 and 4 per cent.

2. Occipital and inguinal lymph nodes are palpable at birth to the extent of 3.95 per cent. and 5.9 per cent., respectively. No cervical, axillary, mental or cubital glands, however, can be felt at birth.

3. Mental, cubital and axillary lymph glands were not palpable in any case throughout the entire series.

4. The high percentage of palpable axillary lymph glands found by Coerper and Baer was, in all probability, the result of identifying as a lymph node the head of the humerus or a nerve trunk.

5. The factors of sex and circumcision and the presence of moist cord stumps have no influence upon the incidence of lymph gland enlargements.

6. The factors of infected eyes and jaundice may have a slight correlation with the palpability of lymph glands.

7. Certain other factors associated with lymph node swellings of the new-born infant may be enumerated in the order of their importance thus: (*a*) infection of the nasal and pharyngeal passageways which causes most or all of the palpable cervical glands, (*b*) prematurity which is correlated with the presence of a higher percentage of palpable inguinal, occipital and cervical lymph nodes, and (*c*) high temperatures (above 100 F.) which are associated, to a slight extent, with the involvement of cervical and inguinal glands.

8. One tenth of the inguinal lymph nodes which are palpable in the new-born can be accounted for by the factors of infection, prematurity, temperature, jaundice, sex, circumcision or the presence of a moist cord stump.

9. One fifth of the occipital glands which are palpable in the new-born can be accounted for by the factors of infection, prematurity, high temperature, jaundice or infected eyes.

10. All of the cervical lymph nodes which are palpable in the first two weeks of life are caused, in all probability, by oral, nasal and pharyngeal infections.

11. The enlargement of inguinal lymph nodes is not due to infection.

12. The new-born infant develops no antibodies against the attached umbilical cord.

13. The new-born infant is not sensitized against the disintegrating proteins of the cord stump.

14. The new-born infant shows no toxic reaction against the foreign proteins of the cord stump.

15. A large percentage of inguinal lymph node enlargement is due, in all probability, to the absorption of sterile foreign protein from the dry cord stump.

20

Reprinted from the American Journal of Diseases of Children
April, 1923, Vol. 25, pp. 319-337

COPYRIGHT, 1923
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET
CHICAGO

2061

Studies on the Fetal Development of the Human Jaws and Teeth.

By S. J. Z. GANTZ, D.D.S., Salt Lake City, Utah.

(From the Department of Anatomy, University of Minnesota; reprinted from the DENTAL COSMOS for February 1922.)

Studies on the Fetal Development of the Human Jaws and Teeth.

By S. J. Z. GANTZ, D.D.S., Salt Lake City, Utah.

(From the Department of Anatomy, University of Minnesota; reprinted from the DENTAL COSMOS for February 1922.)

ALTHOUGH a great many studies have been made on the prenatal development of the teeth and jaws in man, the greater number deal primarily with the histogenesis of these structures, and there is relatively little published material illustrating their general development and topography in the fetal period. Most of the available material on this phase of the subject has been obtained either by reconstruction or by dissection, although there are a few published figures of radiograms of fetal jaws.

Of the reconstructions, the most important are the classical ones of Röse[1] which are limited, however, to the teeth and the related epithelial structures. Among the more important modern figures of dissections are those of Debierre and Pravaz,[2] Vallois and Bennejeant,[3] and Broomell and Fischelis.[4] The first two series are limited to material in the last trimester of prenatal life. The last is much more complete, although the age determinations of some of the younger specimens seem quite open to question. Excellent figures of the mandible and maxillæ at various stages of fetal development have been published by Toldt[5, 6] and by Rambaud and Renault,[7] but these do not include the dental germs.

Published illustrations of radiograms of the fetal jaws seem limited to a single excellent figure of a full-term newborn in the Symington and Rankin[8] atlas and a few rather indistinct figures in Witzel.[9] Thus there still seems to be a place for a selected series of figures from which the student can secure a clear objective picture of the development of the jaw with the teeth *in situ* throughout the fetal period. The object of this study is to supply such a series of illustrations based upon dissected and cleared preparations of the fetal mandible and supplemented by radiograms of skeletal preparations of the mandible and maxilla.

MATERIAL.

A series of 73 specimens, 50 of which were fetuses preserved in 10 per cent. formalin and 23 of which were cleaned and dried skulls, were available for this study. The preserved fetuses were fixed in 10 per cent. formalin and were kept in the same solution. The majority of these were injected with 10 per cent. formalin through the umbilical vein at the time of fixation. The procedure results in the congestion of the terminal arterioles and venules and the capillaries so that these vessels when cleared appear as though distended with a colored injection fluid.

TECHNIQUE.

The preparations illustrated in this paper were made by a special clearing method, which will be described below.

Clearing methods have long been employed by embryologists in their studies, but as far as could be learned from a study of the literature on the subject, no particular attempt has been made to clear the jaws with the teeth *in situ*. The mandible was used in this series, but in most cases dissections were made of the corresponding maxillæ, and it was found that the development was about the same in both jaws, as will be shown by some radiograms of maxillæ farther on.

After a great many experiments with the Schultze and the well-known oil clearing methods, it was found that a slight modification and combination of both gave the best results.

The jaws of fetuses between five months and birth were treated in the following manner: The jaw was dissected from the surrounding tissues and the external and internal plates of bone covering the dental sacs were carefully removed, making sure that the dental sacs were not injured in the process. The specimens were then carried through graded alcohols, beginning with 50 per cent. and finishing with absolute, remaining in each solution for twenty-four hours. They were then placed in a 5 per cent. aqueous solution of potassium hydroxid for about seven days, or until the contents of the dental sacs could be seen when holding the specimen to the light. They were then taken through the alcohols as before and finally cleared in cedar oil. The clearing process requires from one to twenty-four hours, depending on the size of the specimen.

Schultze advised the use of a 3 per cent. solution of potassium hydroxid; other writers have reduced this to a 1 per cent. solution because they found that the tissues were injured in a stronger solution; it was found, however, that a 5 per cent. solution accomplished results faster and without any injury to the tissues.

The jaws of fetuses of four months or younger were treated in a somewhat different manner. No dissecting of the jaw was done until the specimen was cleared, and then it was carried out under a stereoscopic binocular in a Petri dish filled with cedar oil. These specimens were carried through the alcohols, as were the others, and were then cleared in cedar oil without the use of potassium hydroxid.

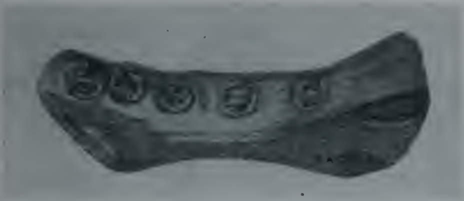
In the resulting specimens, after the treatment as described above, the dental sacs are a bright, reddish yellow, with a dark brown for the dentin and a somewhat lighter brown for the enamel. The bloodvessels are a bright orange or red as though injected with a colored solution. Specimens prepared by these methods may be preserved indefinitely in cedar oil.

DESCRIPTION OF CLEARED SPECIMENS.

A series of selected specimens prepared by these methods are shown in Figs. 1 to 8 inclusive.

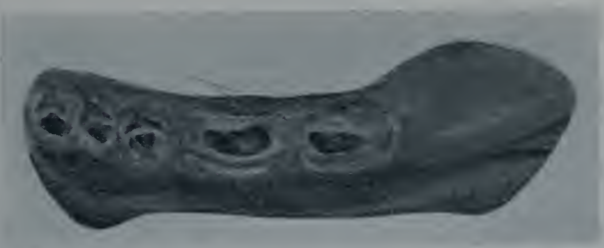
Figure 1 is a drawing of the mandible of a fetus 11 cm. in total or crown-heel length and about thirteen weeks old. This mandible measures 10.5 mm. from the symphysis to the posterior border of the body and 2 mm. from the inferior to the superior border of the body in the region of the mental foramen. Viewed without magnification the five deciduous dental germs are seen hanging "like swallows' nests" from the dental band. In oil, under the stereoscopic binocular with a low magnification, one can clearly see the five balloon-like dental sacs containing the enamel organs suspended by the dental cords, also the dental papillæ growing up from the mesenchymal tissue below. A clear space is seen between the two, which may be an artifact. (In this particular specimen the dental cord of the first molar could not be made out.) The structures described could be seen quite clearly in specimens younger than this one, but this being the simplest form of tooth that was visible in the cleared specimens, drawings of younger jaws would add nothing to this series.

Fig. 1.



A drawing of the buccal aspect of a cleared and dissected mandible of a fetus 11 cm. long and about 13 weeks old. Enlarged approximately 5 times.

Fig. 2.

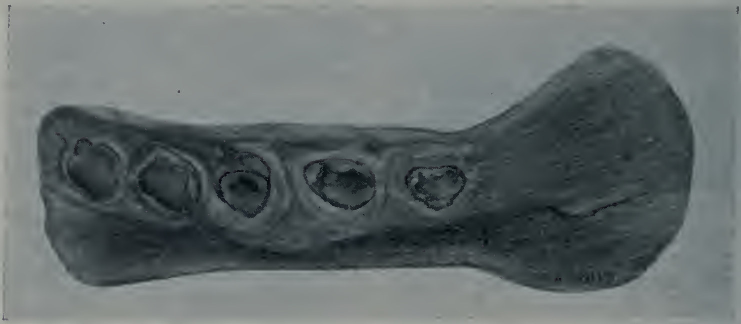


A drawing of the buccal aspect of a cleared and dissected mandible of a fetus 17 cm. long and about 15 weeks old. Enlarged approximately 5 times.

Figure 2 is of a fetus 17 cm. long and about sixteen weeks old. This jaw is 15 mm. from the symphysis to the posterior border of the ramus and 3 mm. from the superior to the inferior border of the body in the region of the mental foramen. The enamel organs of the three anterior deciduous teeth present about the same appearance as those of the preceding figure except that they are somewhat larger. The central incisor, so far as the dental papilla is concerned, has developed the characteristic three elevations on the incisal edge of the young fetal tooth. The deciduous molars have acquired the character of the more mature tooth. Bone development has advanced considerably over the younger stages.

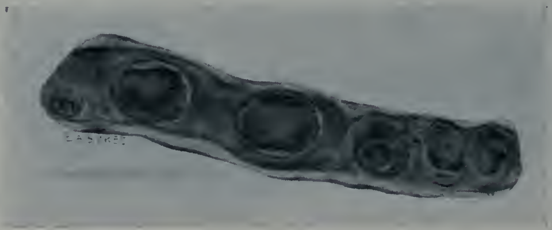
Figure 3 is of a fetus 20.5 cm. long and about eighteen weeks old. The total length of this mandible from the symphysis to the posterior border of the ramus is 18 mm. and its height in the region of the mental foramen is 4.5 mm. The individual character of each deciduous tooth crown is now completely established. In the case of the canine, the enamel organ is still suspended by the dental cord, forming a hoodlike structure over that tooth; and the dental cord, although considerably wasted, can also be seen over the central incisor. There is a well-defined area of calcified material in the mesial cusp of the first molar. Bone has already developed to the extent where it forms bowl-shaped crypts around the dental germs.

FIG. 3.



A drawing of the buccal aspect of a cleared and dissected mandible of a fetus 20.5 cm. long and about 18 weeks old. Enlarged approximately 5 times.

FIG. 4.

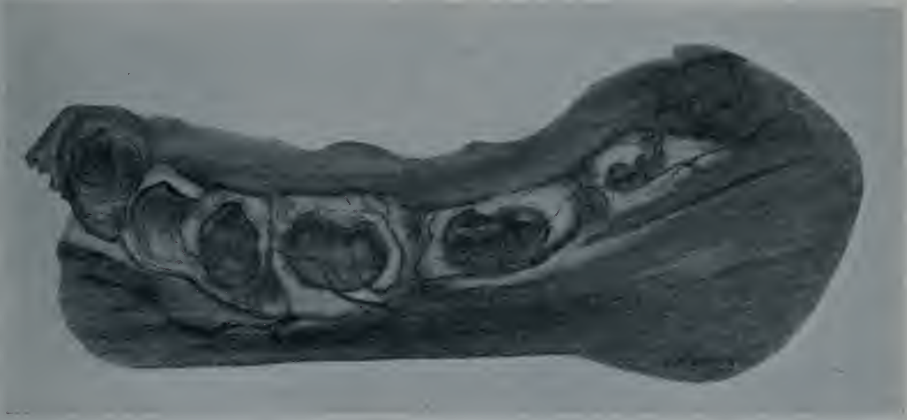


A preparation from the same fetus as Fig. 3, but of the opposite side. The dental germs including the first permanent molar are seen from below.

Figure 4 is of a preparation from the same fetus as the specimens shown in Fig. 3. The soft tissues with the dental germs suspended from them have been dissected away, the drawing illustrating the dental germs pointing upward, making possible the demonstration of the first permanent molar. It will be noted that the specimen, which is characteristic of this period, shows much less development both of the teeth and of the mandible than the specimen figured and described by Broomell and Fischelis[4] as of the fourth month (Fig. 205, p. 266), or the fifth month (Fig. 208, p. 268).

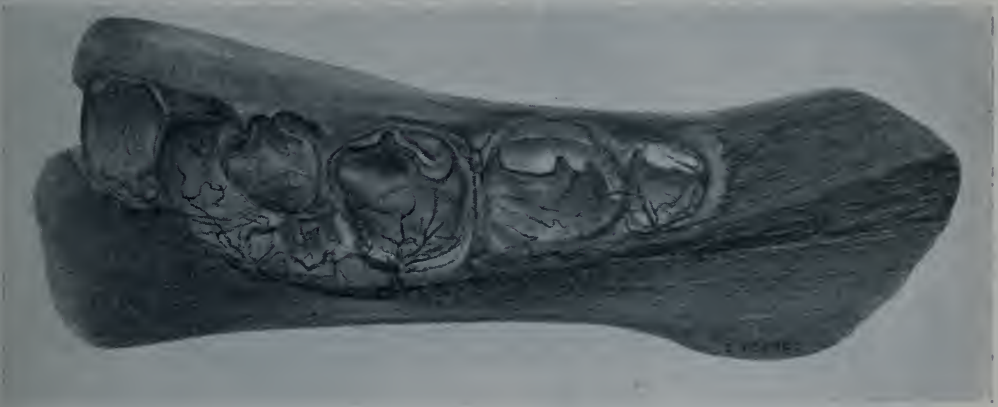
Figure 5 is of a mandible removed from a fetus 32 cm. long or about twenty-four weeks old. The length of the jaw from the symphysis to the posterior border of the ramus is 29 mm. and its height in the region of the mental foramen is 8 mm. Calcification is well established in the central and lateral deciduous incisors, the canines, the first molars and in the mesio-buccal cusp of the second molar. The exact amount of calcification is shown by means of a radiogram of this mandible farther on in this paper. The first permanent molar is of considerable size, although rather shrunken in this specimen. The bloodvessels can be seen coming up from the region of the mandibular canal, or groove, at this stage, and running to and from the teeth and dental sacs; fainter vessels can be seen within the dental papillæ.

FIG. 5.



A drawing of the buccal aspect of a cleared and dissected mandible of a fetus 32 cm. long and about 24 weeks old. Enlarged approximately 4 times.

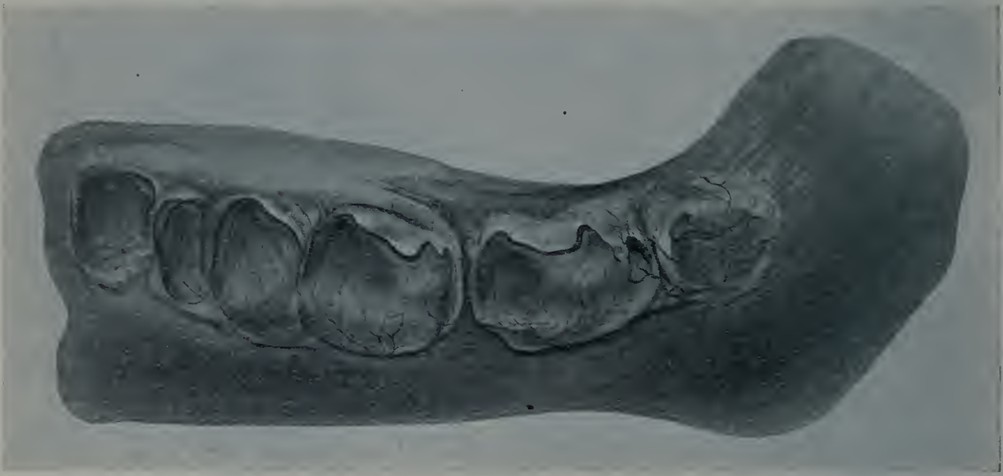
FIG. 6.



A drawing of the buccal aspect of a cleared and dissected mandible of a fetus 41.5 cm. long and about 33 weeks old. Enlarged approximately 3½ times.

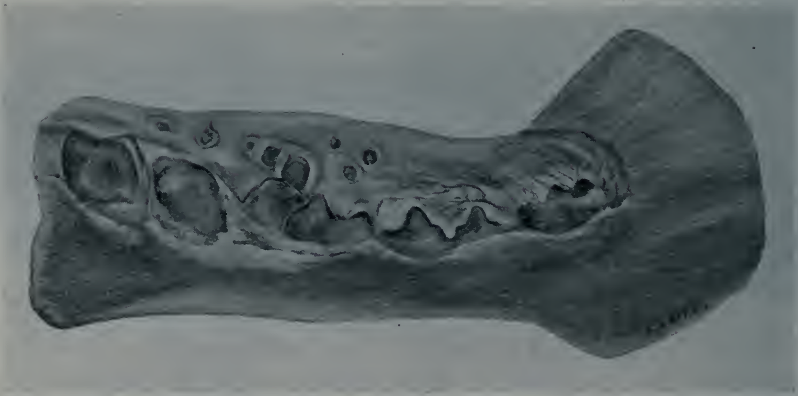
Figure 6 is of a fetus 41.5 cm. in length, in the thirty-third week of prenatal life. The mandible, from the symphysis to the posterior border of the ramus, measures 35 mm., the body of the bone, in the region of the mental foramen, measures 9 mm. in height. In this specimen the central and lateral deciduous incisors, the canines and all cusps of the first molars show considerable calcification, although the latter are still separated from each other. The mesio-buccal, mesio-lingual and disto-lingual cusps of the second molar show definite and well-advanced points of calcification. There is also a small calcified area in the mesio-buccal cusp of the first permanent molar. The bloodvessels are exceptionally vivid in this specimen, particularly in the region of the first deciduous molar. The mandibular vessels are laid bare, and the branches to and from the first deciduous molar are especially clear.

Fig. 7.



A drawing of the buccal aspect of a cleared and dissected mandible of a full-term newborn child. Enlarged approximately 3¼ times.

Fig. 8.



A drawing of a cleared and dissected specimen of another full-term newborn child. Drawn from the lingual aspect showing the epithelial remains of the dental cords. Enlarged approximately 2 times.

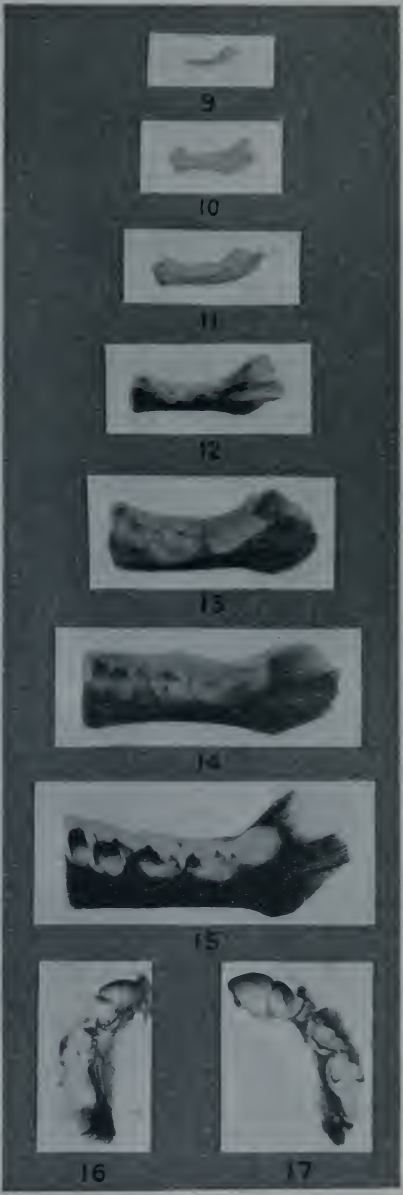
Figure 7 is the mandible of a full-term newborn child. The length of this jaw from the symphysis to the posterior border of the ramus is 39 mm., and the height from the superior to the inferior border of the body, in the region of the mental foramen, is 11.5 mm. The dental sacs seem completely filled by the crowns of the teeth. Calcification has taken place in all the deciduous teeth and the first permanent molar. The cusps of the first deciduous molar have coalesced, forming a solid occlusal surface. All the cusps of the second molar are calcified but they are still separate from one another. There are three small points of calcification in the first permanent molar recorded on the radiogram of this jaw, corresponding to the location of the mesio-buccal, mesio-lingual and disto-buccal cusps of this tooth. Figure 8 is also of the mandible of a full-term new-born child, drawn from the lingual aspect, showing the masses, which microscopic examination proves to be remains of the dental cords.

DESCRIPTION OF RADIOGRAMS.

Radiograms were made of the series of cleared jaws and also of a series of mandibles from dried fetal skulls of various ages. Figures 9, 10, and 11 merely record the exact size and the amount of bone present at various stages of prenatal development. Figure 9 represents the mandible at about two months. Figures 10 and 11 represent the same mandibles which have been shown as cleared specimens Figs. 1 and 2 respectively. Figure 12 is of the same jaw as is shown in Fig. 3. Figures 13, 14 and 15 represent the same mandibles which are shown in Figs. 5, 6, and 7, respectively. They serve to visualize the exact amount of calcification of the deciduous teeth at these respective ages.

Figures 16 and 17 are radiograms of partially dissected maxillæ, as seen from below. Figure 16 is of a fetus 32 cm. in length, the mandible of which is shown in Figs. 5 and 13. In this radiogram one can see clearly outlined the central and lateral incisors, the tip of the canine,

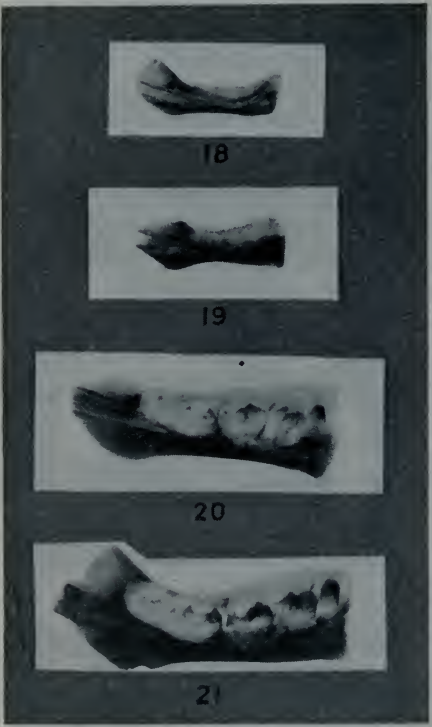
FIGS. 9 TO 17 INCLUSIVE.



A series of radiograms of the mandible illustrating the amount of bone formation and of tooth calcification from the second fetal month to birth. Natural size.

all the cusps of the first deciduous molar and the mesio-buccal cusp of the second deciduous molar. Thus the calcification of the upper teeth corresponds with that of the lower as shown in Fig. 13 of the mandible of the same fetus. Figure 17 shows the maxilla of a full-term newborn. In this specimen also the amount of tooth calcification is equal to that of the mandible of the same fetus as shown in Fig. 15.

Figs. 18 to 21 inclusive.



A series of radiograms of the mandible illustrating the beginning of calcification of the deciduous teeth and the first permanent molars. All natural size.

Figures 18 and 19 illustrate the beginning of calcification of the deciduous teeth in the fetal period. Figure 18 is of a fetus 18 cm. long, and Fig. 19 is of a fetus 22 cm. long. In both these specimens points of calcification can be seen at the summit of each deciduous tooth. In Fig. 19 the central incisor was lost during the preparation of this specimen, but the fact that the other teeth present points of calcification leaves no doubt that the central was as far advanced.

Tomes,[10] in his "Dental Anatomy" of 1889 (p. 139), states that in a former edition of that book he used Magitot's table giving the date of appearance of the various tooth germs; but that he changed to Röse's table which was, in his opinion, more nearly correct. According to the table of Röse, calcification begins when the fetus has attained a length of 24 cm., and then only in the incisors. The last two radiograms seem to indicate that Magitot's table is more nearly correct.

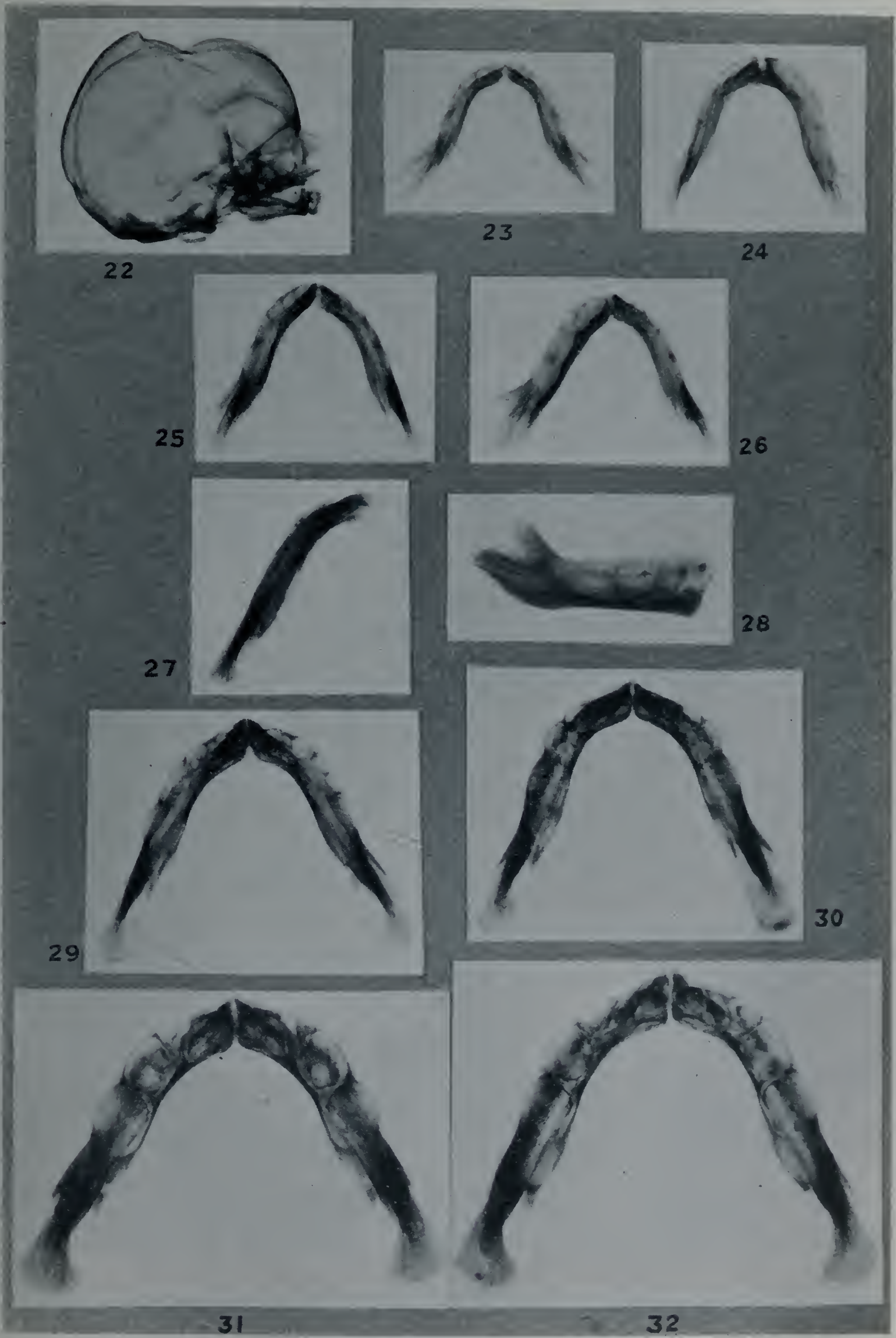
Figures 20 and 21 show the amount of calcification of the first permanent molars in the fetal period. Figure 20 is of a fetus 41.5 cm. in length. The opposite side of this mandible is also shown in Figs. 6 and 14. Figure 21 is of a full-term newborn. The opposite side of this mandible is also shown in Figs. 7 and 15. The points of calcification of the first permanent molars in these two radiograms have been retouched.

Figures 22 to 32 inclusive show a series of radiograms of dried mandibles illustrating the gradual development of this bone and the lower deciduous dental arch. They are from fetuses of the following lengths: Fig. 22, 11 cm., Fig. 23, 18 cm., Fig. 24, 22 cm., Fig. 25, 26 cm., Fig. 26, 30 cm., Fig. 27 and 28, 35 cm., Fig. 29, 41 cm., Fig. 30, 46 cm., Fig. 31, 50 cm. and Fig. 32, 55 cm.

The mandible of the skull shown in Fig. 22 could not be removed, so that the whole skull is shown. Figures 27 and 28 are from a wet specimen, to fill a gap for which a dried specimen was not available. Figure 27 is a dorsal view and Fig. 28 is a lateral view of the same specimen. All the other mandibles in the last series present a dorsal view.

It is hoped that the foregoing material, besides supplying a typical series of illustrations of the fetal development of the

FIGS. 22 TO 32 INCLUSIVE.



A series of radiograms illustrating the development of the mandible from the third fetal month to birth. All natural size.

jaws with the teeth *in situ*, may also show the possibilities of the further application of this technique in the study of these structures.

This work was done under the direction of Dr. R. E. Scammon by the writer while a graduate student at the University of Minnesota. The specimens were demonstrated at the Milwaukee meeting of the National Dental Association, August 15-19, 1921.

The drawings were made by Miss Edith A. Sykes. The radiograms were taken by Dr. H. Holliday of the Dental School.

The writer wishes to express to Professor Scammon his sincere appreciation for the constant readiness to help in all the difficulties that arose during the development of this work, to Dr. Holliday for giving generously of his time in producing the radiographic material, and to Miss Sykes for the careful drawings.

REFERENCES.

[1] Röse. C.: "Ueber die Entwicklung der Zähne des Menschen." *Arch. f. mikr. Anat.*, Bd. 38, 1891.

[2] Debierre, C. et J. Pravaz: "Contribution à l'odontogénie." *Arch. de Physiol.*, 40–83, 1886.

[3] Vallois, H. et C. Bennejeant: "Le developpement du canal dentaire." *Bull. d. Soc. d'Anthropol.* Paris. Sèr. 6, T. 4, 1913.

[4] Broomell, I. N., and P. Fischelis: "Anatomy and Histology of the Mouth and Teeth." Third Edition. Philadelphia, 1910.

[5] Toldt, C.: "Ueber das Wachsthum des Unterkiefers." Zeitschr. f. Heilk., Bd. V, 1884.

[6] Toldt. C.: "Anatomischer Atlas für Studierende und Ärzte." Bd. 1, p. 86, Figs. 192–197. 6 Aufl., Berlin, 1908.

[7] Rambaud, A., et C. Renault: "Origine et développement des os." Paris, 1864.

[8] Symington, J., and J. C. Rankin: "An Atlas of Skiagrams Illustrating the Development of the Teeth, with Explanatory Text." London, 1908.

[9] Witzel, K.: "Entwicklung der Kiefer und der Zähne beim Menschen." Berlin, 1907.

[10] Tomes, C. S.: "A Manual of Dental Anatomy, Human and Comparative." Fifth Edition, London, 1898.

62 Hillcrest Apts.

107

GRADUATE INSTRUCTION IN ANATOMY*

CLARENCE M. JACKSON

The graduate work in anatomy involves two distinct problems: (1) the question of the training of professional anatomists; and (2) the graduate work in anatomy for clinicians. These will therefore be considered separately.

THE TRAINING OF ANATOMISTS

The graduate work desirable for the training of a professional anatomist will depend largely upon the amount and character of his previous study. It is therefore necessary to consider the matter from the beginning of the college work. Let us imagine that at this point a young man has already decided on a future career in anatomy and that he asks for advice in planning his future work. We should point out the various possible paths leading in this direction, and explain that the best plan will vary somewhat according to individual circumstances. For convenience, we may divide the probable course of training into three stages, subject to a certain amount of overlapping and difference in sequence in individual cases. These stages include: (1) the fundamental academic or general college work; (2) the professional work, including elementary courses in anatomy and allied subjects; and (3) the graduate or advanced anatomical work. The essential subject matter for each stage will first be outlined, leaving the question of degrees for later consideration.

Academic or general college work. The present committee is unanimous in considering as an indispensable at least two years of general college work, including the fundamental training in physics, chemistry, and biology (zoölogy), as generally outlined for premedical courses. It is highly desirable (considered essential by Evans, Stockard, Streeter, and Terry) for the future anatomist to extend his general college work to three or four years, which will enable him to obtain much without which he would find himself more or less handicapped in his later career. The additional time would permit a more thorough grounding in the sciences, especially biology, which should include comparative anatomy (Huber, McMurrich, Terry, Jackson) and, incidentally, microscopic technic (Evans, Terry). Dr. Bardeen emphasizes the value of training in physical anthropology. Other desirable subjects mentioned are mathematics (to calculus) and psychology. Of the foreign languages, a reading knowledge of French and German is essentail; Latin and Greek also are desirable. Dr. Terry urges the importance of other cultural subjects, such as history, art, and philosophy, and a thorough training in English.

---

* Report by the Chairman of the Committee on Graduate Instruction in Anatomy, read at the Annual Congress on Medical Education and Licensure, Chicago, March 1, 1921. Published in the American Medical Association Bulletin, 1921, xv, 61–67.

Professional work in anatomy and allied subjects. For a Professional anatomist in a medical school, a thorough preparation in human gross anatomy, histology, and embryology (including neurology) is clearly essential. This would be covered by the courses required for medical students in the best schools. Further elective courses (e.g., topographic anatomy, history of anatomy, etc.) are desirable.

Of the allied subjects, physiology is generally considered the most valuable, on account of the close correlation between form and function in living organisms. Biochemistry is necessary in order to understand the fundamental conditions of morphogenesis. Pathology is also considered essential, since abnormal conditions often throw much light on the normal structure.

As to the necessity for the anatomist to have a knowledge of clinical medicine, there has recently been much discussion and difference of opinion. Considered from the theoretical point of view, it is true that a thorough scientific mastery of anatomy is quite possible without a knowledge of clinical medicine. But, on the other hand, it is very desirable that the teacher of anatomy in a medical school should have an adequate knowledge of how the subject is applied in clinical work. This will make his instruction more efficient, and give him a better insight into various phases of human anatomy. The present committee appears unanimous in considering it essential for the anatomist to have at least a reasonable degree of familiarity with clinical medicine, expressed by Dr. Stockard as an "acquaintance with clinical problems and the general application of anatomical knowledge in medicine and surgery." The majority of the committee believe that it is very desirable for the anatomist to complete the entire medical curriculum.

Graduate or advanced anatomical work. The committee agrees that in all cases the training of the anatomist should include substantial research work under competent guidance in anatomy or some closely related phase of biology. The demonstration of ability in productive scholarship is indispensable. The time required for this will naturally vary in individual cases. The minimum stated is "at least one year" (McMurrich); the maximum mentioned is five years (Huber). Most of the committee members consider two or three years necessary, the majority referring to a requirement equal to that for the Ph.D. as desirable. The possiblities of research work within the medical curriculum will be considered later.

Since teaching is usually an essential part of a career in anatomy, some experience in this line is clearly a desirable element of the training. Dr. Streeter suggests a year of teaching in one of the fundamental sciences immediately following the general college work. Dr. Bardeen recommends a year each in gross anatomy, histology, embryology, and and neurology. If limited in amount (averaging not more than one or two hours daily), so as not to interfere with research work, such teaching is unquestionably of great value in giving a more thorough mastery of the subject matter, as well as useful experience in pedagogic methods. Teaching fellowships should provide such an opportunity for capable advanced students.

The degree question and time requirements. All of us would agree that for the training of an anatomist the essential thing is the work previously outlined. This should be done in one of the better institutions, insuring proper facilities, guidance, and inspiration. With this proviso, the question of where the work was done (college, medical school, or graduate school) is of comparatively little importance, as are likewise the degrees obtained (B.S. or B.A., Ph.D. or M.D.). The essential point is to train an anatomist who is a productive scholar and a good teacher. The degrees themselves are of value only in so far as their requirements may outline a systematic and desirable plan of work, for which the degree is the goal and the certificate of achievement.

If we look over the work outlined here as desirable for the training of the anatomist, we find that the general college work will usually lead to the bachelor's degree (at once if four years are taken; one or two years later, if only three or two years of general college work are taken, followed by entrance into a medical school on a "combined course" in arts and medicine). We likewise find that the essential fundamental work in anatomy, together with the desirable allied laboratory and clinical subjects will correspond roughly to the requirements for the M.D. degree. And finally the necessary proficiency in research work corresponds approximately to the requirements for the Ph.D. degree. (The Master's degree, M.A. or M.S., may often be taken to advantage on the way toward the Ph.D.)

In general, therefore, it may be said that in terms of degrees, the *equivalent* of both the M.D. and the Ph.D. is desirable. So far as the anatomists of the present generation are concerned, however, very few have actually taken both degrees. In most cases, after the general college work, one of two roads has been followed: the medical curriculum leading to the M.D. degree, or graduate work leading to the Ph.D. degree. It so happens that of the present committtee of nine anatomists six followed the former path, and three the latter. What usually happens is that the anatomist with the Ph.D. makes up his deficiency by supplementary study in allied medical work; while the M.D. as a rule finds it necessary to devote himself to additional research work for a considerable period before he becomes a competent anatomist.

Dr. Evans protests strongly against the current tendency to consider the Ph.D. degree as representing a more thorough training in research work than does the M.D. degree. He insists that research work should be made an essential part of the requirements for the M.D. degree, making space in the curriculum for this by reducing the specific requirements (especially in the clinical specialties) and introducing a liberal elective system. While in view of the prevailing conditions in American medical education this may appear a "counsel of perfection" not likely to be realized in the immediate future, many of us would agree that a liberalizing of the medical curriculum in this direction is an outstanding need. The principle of electives in the medical curriculum is already well established to a limited extent in several of the leading medical schools and should be extended to all. This applies especially to the new fifth-year requirement, which may usually be met either by a hospital internship or by a year of research work in any well-equipped medical laboratory. This substitution should always be permitted.

Assuming that the medical curriculum provides liberal electives and adequate facilities for research work, it is of interest to note the probable minimum time within which it would be possible to obtain the training which we have outlined as essential for the anatomist. Table 1 may perhaps make clearer the principal points in this con-

REQUIREMENTS FOR TRAINING IN ANATOMY

Solid lines represent years required for degrees; broken lines, electives.

Advanced or research work in anatomy (leading to Ph.D. degree)						6 Electives in four, five, six years of Medicine	7 Research year substitute for intern.	8 Additional year of research
Elementary anatomy and allied subjects (leading to M.D. degree)			3 Freshman medical	4 Sophomore medical (20 per cent elective)	5 Junior medical (30 per cent elective)	6 Senior medical (50 per cent elective)	7 Intern year (100 per cent elective)	
General college work (leading to B.S. or B.A.)	1 Freshman college	2 Sophomore college	3 Junior college (combined	4 Senior college course)				

nection. The work is classified according to the three grades or stages previously considered. The general college work requires two to four years, the medical work four (or five) years, and the graduate or research work three years. There are two obvious possibilities of reducing the total time by overlapping or "telescoping" in the three grades of work. In the well-known "combined course," the first and second years of medicine may replace the junior and senior years of general college work. Furthermore, if a liberal elective system prevails, it should be possible to obtain practically a year (supplemented perhaps in vacation) of advanced or research work in anatomy during the four years' medical course, and a full year of research in lieu of the internship. An additional (third) year of research work in anatomy would complete the desirable quota, giving in all a training corresponding to the usual requirements for the B.S., M.D., and Ph.D. degrees in a minimum of eight years. This would be possible only under the most favorable conditions, however. Under ordinary circumstances it would be more likely to require nine or ten years before the anatomist could consider himself fully equipped for an independent career. This is particularly true if it has been necessary, for financial reasons, to engage in teaching for more than the minimum amount of time.

The financial or economic aspects of a career in anatomy constitute an important problem whichcan not be ignored. As Dr. Streeter points out, the anatomist in order to acquire an adequate training must make an expenditure of approximately $10,000, and must give eight to ten of his best years. There should be a fair return on the investment. The remuneration to be expected, under present conditions, begins with an instructorship at about $2,000 and leads ultimately to a professorship at perhaps $5,000. In comparison with the financial rewards in the practice of medicine, this is insufficiently attractive. It is generally recognized that conditions must be materially improved or the departments of anatomy (likewise physiology and pathology) will soon deteriorate, to the ultimate detriment of medicine in general.

The unsatisfactory status of the fundamental medical sciences has recently been shown by a committee of the National Research Council[1] and emphasized by Dr. Wilson.[2] The latter endorses, as a possible remedy, Keith's view that laboratory men should be permitted to devote a part of their time to clinical practice, which would increase their income as well as enable them to give more practical instruction to medical students.* Our anatomy committee regards this plan as a reactionary proposal, which would injuriously affect the future development of anatomical science. Better a half-starved full-time anatomist than a well-fed part-time practitioner! Clinical anatomy is a legitimate and desirable field for scientific work; but it should not be required of the anatomist in order to eke out his income by fees from patients. The wise solution of the problem lies rather in the improvement of conditions so as to enable talented men to devote themselves whole-heartedly to anatomical teaching and research. As Dr. Stockard puts it, "The most important object should be to attract men of high ability with the proper hereditary complex, such as now go into medical practice and the business fields."

GRADUATE WORK IN ANATOMY FOR CLINICIANS

The committee recognizes the necessity for further basic work in anatomy by progressive clinicians, and favors coöperation with them by providing so far as possible the necessary facilities. Aside from general practitioners who desire merely brief review work (chiefly in dissection), opportunities should be provided especially for those preparing to specialize in some clinical field, and who desire to make an extensive and intensive study of the anatomy (including histology and embryology) of the regions concerned. As a rule, this does not require the organization of additional courses, but merely the opportunity for individual work, under supervision on materials already available in the laboratory. This should culminate in research work on anatomical problems in which the clinician is especially interested. In some cases it may be desirable to add to the anatomical staff, as part-time or full-time members, some of the younger clinical specialists who are willing to devote time to the development of this work in teaching, making special preparations, and so forth. Such work in clinical applied anatomy

---

*That the committee has misunderstood this proposal is evident from the following statement in a letter from Dr. Wilson to the Chairman of the committee: "I have gone carefully over my article on 'The Present Status of Preclinical Branches,' and I am at a loss to see how you could have interpreted my statements or the quotation from Keith as suggesting that preclinical men should engage in private medical practice. Keith says: 'At *medical schools* they should hold clinical appointments.' I say: 'Should not the *University Hospital* provide contact with patients?' We both suggest that such clinical contact will make the man a better teacher of future practitioners of medicine and that his ability to meet the clinician on the latter's own ground will gain him greater respect. But surely, both these are far from the 'straw' anatomist-practitioner, which the report of your committee so valiantly disposed of."

should be fully encouraged, and should lead to results worthy of publication.

BIBLIOGRAPHY

1. An investigation of conditions in the departments of the preclinical sciences. Report of a committee of the Division of Medical Sciences of the National Research Council. Jour. Am. Med. Assn., 1920, lxxiv, 1117–1122.

2. Wilson, L. B.: The present status of preclinical branches. Chicago Med. Rec., 1920, xlii, 465–469.

208.

Reprinted from SCIENCE, pages 537-546, Vol. LVII, No. 1480, May 11, 1923.

DYSTROPHIC MORPHOLOGY AND ITS SIGNIFICANCE[1]

AMONG the environmental factors which influence the structure and functions of the living organism, nutrition is of primary importance. One of the most fruitful methods of studying the process of nutrition is that of inanition. By withholding or decreasing the normal diet (total inanition) or merely one or more of the essential nutritional elements (partial inanition), we may observe effects which throw much light upon the normal process of nutrition from the standpoint of physiology, of pathology or of normal morphology. It is with the morphological aspect of the problem that we, as anatomists, are primarily concerned. We desire to learn the significance of the form and structure of the living organism and the factors concerned in its morphogenesis.

Experimental work by many investigators in this field during the past century has resulted in a large number of widely scattered data concerning the effects of inanition upon the growth and structure in numerous species. These effects of inanition have been extensively and carefully studied, not only in the vertebrates, but also among the lower organisms, the invertebrates and the plants. It may therefore be profitable to review briefly some of the principal results of inanition in these lower forms, partly because they are less well known to anatomists in general and partly because certain aspects of the problem are more clearly revealed in these simpler organisms. In general, only those phases will be considered which appear of most significance in comparison with the results in the higher animals, including man.

---

[1] Presidential address, American Association of Anatomists, Chicago, March 29, 1923.

EFFECTS OF INANITION IN PLANTS

Plants in general, much more than animals, appear susceptible to modification by various external factors, including the food supply. It is difficult to summarize briefly the principal morphological effects of inanition upon plants on account of the wide range in the character of these organisms and the great differences in their mode of nutrition. In general, however, it is clear that the effect of inanition is to restrict or inhibit their growth during the developmental period, often resulting in premature development with the production of marked abnormalities of form and structure. In the poppy (*Papaver*) an inheritance of some of the experimentally produced variations is claimed (De Vries, Hoffman, Rignano). In later stages the plants are usually less susceptible; but sooner or later a deprivation of nutriment will usually produce protoplasmic atrophy and progressively degenerative changes in the cells and tissues, finally resulting in the death of the organism. Of the cell constituents, the formed storage products (starch, oil, etc.) are usually consumed first; then the cytoplasmic structures are attacked; lastly the nucleus, which is the most resistant.

These effects are produced not only by general or total inanition (either complete or incomplete) but also often in a strikingly characteristic manner by partial inanition, when there is a marked deficiency of only one (or a few) of the numerous essential factors of plant nutriment. Lack of any one of these factors—water, calcium, potassium, magnesium, iron, phosphorus, sulphur, manganese, nitrogen, carbohydrates and possibly vitamins—will cause stunting of growth with variable degenerative cell-changes. These are expressed by morphological and physiological derangements, often resulting ultimately in the death of the organism. The effects are apparently most severe in the case of phosphorus or nitrogen deficiency.

In addition to the deleterious effects more or less common to all these partial deficiencies, there are in each case certain peculiarities due to the special functions which each of the food-elements normally performs. These peculiarities appear also to vary considerably in different classes of plants.

Thus water deficiency is usually expressed promptly by characteristic changes in form and structure of plants on account of its fundamental importance in morphogenesis and vital structure, as well as in transportation. Of the various salts, those of calcium, potassium and magnesium are especially essential for chlorophyll production and starch formation. Phosphorus appears to be more concerned with the transformation than with the origin of carbohydrates. Cellulose formation proceeds in the absence of phosphorus, but is impossible without calcium. Mitosis may occur in the absence of calcium or of magnesium, but not without potassium or phosphorus. The process of inflorescence and the development of the sexual organs in general appear to be unusually susceptible to the effects of malnutrition and in some cases (especially in fern prothallia) a deficiency of calcium or nitrogen may influence sex by inhibiting the development of the female organs (archegonia).

EFFECTS OF INANITION IN PROTOZOA

Some of the more important results of inanition among the protozoa may be indicated briefly in relation to changes in body size, endoplasm and ectoplasm, nucleus (macronucleus and micronucleus), reproduction (cell-division and conjugation) and recovery upon refeeding.

Change in size and form of the body—All the evidence shows a marked reduction in the size of protozoa during inanition. The maintenance of the original size in *Noctiluca* is merely apparent, the increase in peripheral vacuoles masking the decrease in cytoplasm. The recorded data indicate a decrease in length to about one half of the original in *Paramecium,* one fifth in *Stentor* and one tenth in *Dileptus* and *Pleurotrichia.* Thus in these extreme cases the volume may be reduced to less than one per cent. of the original. The rapidity of the loss varies according to temperature. There are also more or less marked and variable changes in form accompanying the diminution in the size of the body.

Changes in the endoplasm—The cytoplasmic changes at first appear chiefly in the endoplasm, which becomes progressively reduced in amount and transparent, on account of the disappearance of the food-vacuoles and similar inclusions. In the later stages of inanition a progressive vacuolation of the endoplasm has been described in various species by all recent observers except Lipska. Such vacuolation of the endoplasm apparently does not occur in *Noctiluca* and *Pleurotrichia,* however, and Lipska's results indicate that even in *Paramecium* it is probably only an indirect effect of inanition, being due primarily to other environmental factors.

Changes in the ectoplasm—In all cases the cell-membrane and associated ectoplasmic structures (cilia, trichocysts, cytopharynx, etc.) appear more resistant than the endoplasm, but in the later stages of inanition they also may be attacked and partially resorbed. Associated with these regressive changes there is a progressive decrease in motility and in other vital phenomena.

Nuclear changes—The nucleus in general is much more resistant than the cytoplasm, but may show changes in form with loss of chromatin content. In forms such as *Paramecium*, with macronucleus and micronucleus, the former shows more distinct changes. In the earlier stages of inanition it frequently elongates and enlarges. Later it usually divides and may show degenerative changes, with granulation, vacuolation, fragmentation and variable extent of resorption. The micronucleus usually persists practically unchanged, although rarely it may divide with reunion of the daughter nuclei. This persistence of the nucleus is a factor of great importance for the survival of the organism during periods of inanition. The less important constituents of the organism are usually consumed first, the most essential apparently survive longest. The persistence of the nucleus during starvation recalls a similar behavior when living cells are engulfed and digested (*e.g.* by *Trichosphaerium,* according to Schaudinn) and in trypsin digestion experiments upon dead cells. This may be of significance as indicating the presence of similar enzymes during the autolysis of cells in starvation.

Effects on reproduction—The relations of inanition to reproduction in protozoa have attracted much attention. Many observers have noted an apparent stimulus to division resulting from a brief period of starvation. R. Hertwig, however, observed that while under certain conditions fasting protozoa may divide more readily than well nourished, as claimed by Jickili and others, this does not occur as a general rule. In *Paramecium,* which has been more extensively studied, divisions occur to a variable degree in the early stages of inanition, but rarely or never in the later stages. According to Hertwig's theory, inanition upsets the cell-equilibrium as expressed by the nucleus-plasma ratio; but the relative increase in the nucleus may be equalized later by a reduction in chromatin, associated with the process of conjugation.

Rolph, who proposed a nutritive theory of sex, claimed that conjugation occurs in protozoa when conditions result in an interference with their nutrition. Thus sex is considered as primitively a form of hunger, which drives the organism to engulf its neighbor ("isophagy"). A similar theory of sex was elaborated by Geddes and Thompson. The studies of Maupas and of numerous more recent investigators, however, have shown that the life cycle of the protozoa, with its phases of sexual and asexual reproduction, is apparently a very complicated process, involving both internal and external factors. Among the latter, inanition is doubtless an important factor, which under certain conditions may induce conjugation. This was observed by Maupas and others in numerous species of Infusoria. Hertwig discovered that when low temperature cultures (which have a relatively large nucleus) are placed at a high temperature and kept without food, an artificial depression is produced which leads to conjugation. This was confirmed by Prandtl for *Didinium,* and by Popoff for *Epistylis.* Conjugation has been observed in the earlier stages of ordinary inanition in *Paramecium* by Kasanzeff, Wallengren and Chainsky; but Calkins and Lipska found inanition very unfavorable to conjugation. It is evident that further research is necessary in order to clear up this fundamental problem.

Recovery upon refeeding—The protozoa show an astonishing capacity for recuperation upon careful refeeding after inanition. Maupas found that an atrophic *Stentor* regained its original size in two days of abundant realimentation, which evidently involved an increase of over one hundred times its reduced volume. Joukowsky observed a similar remarkable capacity for recuperation in *Pleurotrichia.* In *Paramecium* Wallengren found a normal recovery possible, even in the greatly vacuolated condition after fifteen days of inanition. Lipska, however, found recovery in general possible only up to four or five days of inanition. The process of recovery is the inverse of that during inanition, and cell-divisions begin after three to five days of refeeding. Jennings noted that variability in size is increased during refeeding, some individuals recuperating more rapidly than others; but the normal condition is eventually restored.

EFFECTS OF INANITION AMONG THE HIGHER INVERTEBRATES

Although it is impossible to summarize satisfactorily the effects of inanition upon such a large and varied group of organisms as those represented by the metazoan invertebrates, it may be profitable to review briefly some of the principal features involved.

Effects on body weight and size—As pointed out by Pütter, the possible decrease in dimensions during inanition is much less in those forms having a firm skeleton (*e.g.,* Arthropoda). The maximum possible reduction in body weight and size varies greatly among the higher invertebrates, ranging from fifteen or twenty per cent. in some Arthropoda to over ninety per cent. in some coelenterates and planarians. Among coelenterates, *Hydra* is reduced to one seventh or less in length; the jellyfish *Aurelia* to one fourth and *Cassiopea* to one twenty-fifth of the original volume. Planarians (flatworms) may be reduced one twelfth in length and to one three hundredth in volume. In the snail *Helix,* the loss in weight apparently varies from eleven to fifty per cent. or more, according to species and conditions, with much individual variation. Among the Arthropods a loss of seventy-five per cent. in weight is recorded for the water-flea *Daphnia* and of fifteen per cent. for the crayfish *Astacus*. Great variation has also been found among the insects.

There are relatively few data on the loss during inanition in larval stages. The larvae of the sea-urchin *Strongylocentrotus lividus* may decrease to half the diameter of the original ovum. *Chortophaga* nymphs lose twenty to twenty-five per cent. and the tent-caterpillar (*Clisiacampa*) thirty-five per cent. The remarkable reduction (to one six hundredth) in the larva of the beetle *Trogoderma* is apparently exceptional. The loss during the pupal stage in general appears relatively slight.

Effects on the form of the body—During inanition the body is not only reduced in size, but also frequently more or less changed in form. *Hydra,* for example, becomes at first abnormally elongated, later greatly contracted and relatively broader. The water-flea *Daphnia* presents a peculiar modification of body form attributed to malnutrition and said to be hereditary (Woltereck). In the sponges, the coelenterates and the planarians the changes are remarkably great, not only in external form but also in corresponding internal structure. The so-called "reduction" process in these forms more or less resembles a reversal of the developmental process, which will be discussed later. In planarians the involution frequently involves the posterior portion of the body to a greater extent, resulting in a relative enlargement of the head region. This is also true of the nemertine worm *Lineus lacteus,* but not of *Lineus ruber,* which illustrates the differences which may occur between species.

Changes in various organs and tissues—It is a remarkable fact that the various organs and tissues of the invertebrate body differ greatly in their resistance to inanition. Some undergo changes very quickly, others only after longer periods, and still others show a remarkable resistance. There are also differences in the extent of atrophy, as well as the order of sequence.

In the medusa *Cassiopea* the loss is almost entirely at the expense of the gelatinous ground substance; while in sponges, on the contrary, this substance is increased in amount. The ectodermal structures are more resistant but they atrophy to a variable extent in different regions. In planarians the intestinal epithelium, eyes, pigment tissue and sexual duct systems are affected relatively early; the muscles atrophy later, while the gonads and nervous system persist with great tenacity. In *Lineus* the relative resistance of the various tissues is somewhat similar to that in planarians. Although among the higher invertebrates the skeleton is usually unaffected by starvation, in the snail *Helix* the calcareous shell is attacked as well as the soft tissues; while in sponges the results appear variable. Calcium deficiency usually causes involution of the invertebrate calcareous skeleton, both in larval and adult stages. In the reproductive passages of *Helix* the non-glandular parts appear more resistant than the accessory albuminous gland, which undergoes an enormous involution. While the gland cells are greatly reduced, however, the associated "parenchyma" (stroma) nuclei persist and proliferate by amitosis.

Effects on the gonads and sex—The effects of inanition upon the reproductive system and process have aroused much interest and have been carefully observed in various invertebrates as well as in other organisms. In forms where the process of reproduction may be either asexual (by budding, fission or parthenogenesis) or sexual, the tendency of abundant nutrition is to favor asexual reproduction; while inanition or other unfavorable environment usually occasions a change to the sexual form, in many cases especially favoring the development of males. The gonads themselves are usually very resistant to starvation, being (like the nervous system) as a rule among the last of the organs to undergo involution. There are, however, evident variations in different species and individuals.

Among sponges the process of involution during inanition frequently results in the formation of numerous small bodies ('gemmules'), from which new individuals may be reproduced later. In *Hydra* budding is inhibited but the gonads, especially the testes, may mature in spite of the atrophy of the body as a whole. The predominating development of testes in *Hydra* during inanition was emphasized by Nussbaum, Schultz and Berninger, but was denied by Hertwig, Whitney, Hänel, Krapfenbauer and Frischholz.

In planarians asexual reproduction is inhibited by inanition and there is a return to sexual reproduction; but the 'cocoons' are reduced in size and the number of enclosed young markedly diminished. In the nemertine worm *Lineus* the gonads undergo partial involution, but some areas (likewise the ducts) are very persistent.

In the rotifers (wheel-animalcules) Leydig noted that inanition causes prompt atrophy of the ovary and a tendency to production of males. Nussbaum concluded that in the rotifer *Hydatina* underfeeding in the *phase preceding the ripening of the ovum* tends to produce male offspring. This was confirmed by Lennsen but opposed by Whitney. Shull concluded that sex in *Hydatina* is determined by both internal and external factors, but that the production of males during inanition is probably only an indirect effect.

The relation of nutrition to sex has also been studied extensively in the crustacean water-fleas by Leydig and others. The change from parthenogenetic to sexual mode of reproduction under unfavorable conditions (especially inanition) in this group was noted by Kerhervé, Cuenot and Issakowitsch. More recently, the internal factors have been emphasized, although it is admitted that the hereditary tendency may be influenced by external factors, such as malnutrition, especially during the labile period of the ovum. Green recently concluded that in *Simocephalus* the sex is probably predetermined in the ovary, but is also subject to environmental influence, though probably not through starvation.

Among the insects the relations of nutrition to sex have been noted especially in the aphids (plant-lice), the Lepidoptera and the Hymenoptera. The appearance of winged male forms in aphids as a result of underfeeding was noted by Kyber (1813), Leydig and others. The same phenomenon in the grape-louse *Phylloxera* was found by Keller and Behr. Thus apparently all observers admit the effect of unfavorable environment, especially underfeeding, in causing the cessation of parthenogenesis and the appearance of males and sexual reproduction among the aphids. The conditions in this group therefore form strong evidence supporting the theory of nutritional sex-determination.

In the Lepidoptera, Treat observed a preponderance of males as a result of underfeeding the larvae of certain butterflies. This was not confirmed by Poulton, although he admitted that a lesser resistance to inanition in the female larvae might result in a selective mortality with survival of a relatively larger number of males. This, of course, is not strictly a process of sex-determination, but rather of sex-survival. In the underfeeding experiments by Kellogg and Bell on the silkworm *Bombyx* and by Guyénot and Loeb and Northrup on the fruit-fly *Drosophila,* no effect on the sex-ratio was observed.

Among the termites and Hymenoptera the sex is known to be determined by fertilization, the unfertilized eggs producing the males. The diet, however, determines the development of the female reproductive tract, which in the few larvæ well-fed (with "royal diet") becomes functionally developed, producing the "queens"; while in the less richly nourished larvæ the reproductive tract remains rudimentary, producing the "workers" of which there may be different kinds, depending upon the amount of food available. There is some evidence, however, indicating that in wasps (and possibly other Hymenoptera) the sex-ratio may be affected by nutrition, but this is somewhat uncertain.

Among the invertebrates in general we may therefore conclude from the available evidence that malnutrition tends to favor the sexual, rather than the asexual, mode of reproduction. Furthermore, especially in Hydra, rotifers, daphnids and aphids the sex-ratio is at least to some extent subject to environmental influence, inanition tending to produce a preponderance of males. Wilson concluded that nutrition is one factor which may determine sex. Schultze reached this conclusion for Hydra and Hydatina, but felt less certain regarding the daphnids and aphids. How this influence becomes effective, however, is still a matter of uncertainty. The whole question requires further investigation, especially in the light of the recent theory of sex-determination by the accessory chromosome.

Effects on cell structure—We have noted that the effect of inanition is to produce a variable decrease in the size of the body as a whole, which is found to involve a variable reduction in the various parts, organs and tissues. This, of course, depends ultimately upon the changes in the underlying units, the component cells of the organism. Some cells are destroyed and absorbed, others persist more or less changed. From his study of the histological changes in *Hydra* and planarians during the involution process of inanition, Schultz inclined to attribute the marked decrease in size of the body to a decrease in the number of cells, those persisting being practically unchanged in size. The preponderance of evidence is against this view, however. Especially in the adult organism, all the cells of the body during inanition tend to undergo more or less atrophy. The extent and character of this atrophy vary in the different tissues and in different cells of the same tissue. The decrease in the size of the body is therefore due partly to the complete disappearance of cells and partly to an atrophy of those persisting.

During the process of atrophy the cytoplasm of the starving cells undergoes in general a series of characteristic changes, first losing its stored food material, pigment, mitochondria and various inclusions. Later the cytoplasm of the cells often fuses into a syncytium. Vacuolation usually appears, with progressive decrease in amount of the cytoplasm, and terminal disintegration with complete absorption in the case of some of the cells. There is usually an earlier stage of reduction in size (simple atrophy) and a later stage of degeneration.

The nucleus is usually more resistant than the cytoplasm, giving a higher nucleus-plasma ratio. At first the nucleus may even enlarge, but later it tends to shrink (pycnosis) with perhaps ultimate fragmentation, karyolysis and final absorption. The reduction in cytoplasm and relative increase in nuclear size frequently gives the atrophic tissue an embryonal appearance.

Some further special features in the atrophic cell changes may be reviewed briefly. As noted by Terroine from the chemical viewpoint the fat changes show great variation among species and individuals. While fat in general is quickly absorbed during inanition, in the vitelline gland cells of planarians it is tenaciously retained, disappearing only when the cells undergo final necrosis. In planarians and molluscs the nerve cells may show certain degenerative changes, although the nervous tissue as a whole is remarkably resistant. It may be noted that apparently the final absorption of the degenerated cells in the various tissues is usually accomplished by simple solution in the interstitial tissue fluids; although phagocytosis has been noted in sponges, sea-urchin larvae and especially in the case of the nemertine worm *Lineus*. The process of phagocytosis is said to occur also in the metamorphosis of insects.

Some specific changes in cell-structure are noted during various forms of partial inanition. Thus calcium deficiency may loosen the intercellular attachments but it does not affect the ciliary mechanism and apparently permits mitosis to continue in the embryonic tissues of various invertebrates. Phosphorus and potassium, however, are evidently necessary for mitosis, as in plants. In addition to the mineral salts, certain proteins, fats or carbohydrates, water, etc., are doubtless essential to life, but we have as yet little data upon the morphological effects of their deficiencies among the higher invertebrates.

Effects on the developing organism—The effects of inanition upon the developing invertebrate organism, especially during the earlier embryonal stages in many respects often differ markedly from those previously described for the adult. The embryonal cells have a characteristic tendency to growth and differentiation which may enable certain organs and tissues not only to persist but even to enlarge and develop at the expense of the remainder of the starving organism. This is true for general inanition and is also especially evident during various forms of partial inanition. Thus in many cases it is evident that a deficiency in one limiting factor does not necessarily altogether inhibit the development of the invertebrate organism when that factor is exhausted, but occasions instead a disproportionate, abnormal growth, the extent and character of which will vary according to circumstances.

On the other hand, in many cases the developing embryo or larva (in some species even the adult organism) tends to undergo during inanition a series of retrogressive changes more or less reversing the normal order of development. This process (technically called 'reduction') was apparently first described by Lillie (1900) in *Planaria maculata.* It is often well marked in sponges, coelenterates and planarians, though apparently rare in the more highly organized invertebrates. Even in the lower invertebrates, however, there is some question as to whether the (often remarkable) resemblance of the atrophic organism to the earlier embryonic stages may not be more apparent than real. But in many cases these atrophic remnants are actually able, under proper conditions of nutrition, to regenerate the normal structure of the organism. Child concludes that starvation results in morphological rejuvenation, followed by physiological regeneration upon refeeding.

The relatively great resistance to inanition usually offered by the gonads has already been mentioned for adults. This applies also in some cases to the developing organism, so that sexual maturity may occur in undersized bodies as a result of underfeeding (*e.g.,* silkworm and certain bees). But in others (starfish) sexual maturity is reached only upon the attainment of a certain body size, or the development of the gonads may even be entirely inhibited by inanition (fruitfly).

The sex of the offspring, as already mentioned, may also be influenced through the effect of inanition upon the germ cells in the larval stages, particularly at certain critical periods (rotifers, daphnids, aphids, etc.). In some insects sexual maturity appears to be determined entirely by larval nutrition, in others chiefly by the adult nutrition.

Underfeeding during the larval period may also result in undersized adults (various insects) and also sometimes in marked structural modifications (pigmentation, etc.). In some cases these acquired characters appear hereditary, at least for a few generations (as found by Woltereck, Pictet, Kellogg and Bell); although ultimately upon adequate diet there is an evident tendency to return to the original condition.

The experiments with media or diets variously deficient have shown that compounds of P, K, Na, Ca, Mg, Fe, S and Cl appear necessary for development, growth being inhibited or variously perverted when the amount stored in the ovum is exhausted, unless a supply from without is available. Remarkable results in this field have been obtained by Herbst, Loeb and others. The marvelous effect of fat upon the development of the reproductive tract in the female Hymenoptera also illustrates the morphogenetic potency of a single dietary factor. As to other forms of partial inanition, Baumberger holds that protein is in general the limiting factor in the growth of insects. The fruitfly *Drosophila* apparently requires yeast as well as sugar for growth and other insects living on fermenting substrata of low protein content usually feed on the microorganisms present. Little or nothing is known concerning the possible requirement of vitamins by the invertebrates in general.

Regeneration during inanition—In many of the invertebrates indications of regenerative activity may be observed in certain cells or regions during the degenerative process of involution. Driesch noted that the reserve materials of the body which are consumed during starvation may be used to build up other parts of the organism. Thus in daphnids, crustacea and insects repeated ecdysis (moulting) with regeneration of a new exoskeleton and appendages may occur during total inanition. This regenerative process occurs notably in the lower invertebrates such as the sponges and coelenterates and has been studied especially in planarians by Morgan, Schultz and others. Here the starving organism exhibits the remarkable capacity to regenerate large portions of the body, such as the head, with all its parts, pharynx, nerve ganglia, musculature and excretory system. Thus even during starvation regeneration may restore a complete normal individual of much smaller size. In this process there is an extensive involution of the older tissues to furnish material for the regenerated parts.

Recovery upon refeeding—In general it is possible for the starving invertebrates to recover their normal size and structure upon appropriate refeeding if the process of involution has not proceeded too far in degeneration. This applies also to partial inanition. In sponges, for example, the skeleton is reformed upon restoring calcium carbonate to the medium. In planarians regeneration of the gonads is possible even when they have nearly disappeared after three or four months of inanition. In the gland cells of the snail *Helix* starved five months, evidences of recuperation were found by Krahelska even after only two days of refeeding. *Drosophila* (fruitfly) larvae are capable of normal development even after long periods of retardation on inadequate diet; and in this form, as likewise in the larvae of the beetles *Trogoderma* and *Tribolim,* the normal period of 'life may be greatly extended by retarding the developmental process through alternate periods of fasting and refeeding. Underfed larvae of the moths *Acronyeta* and *Bombyx* produce smaller pupae and adults, the effect in the case of *Bombyx* being carried over to the second and third generations.

COMPARISON WITH VERTEBRATES

Comparison of the results of inanition among plants and invertebrates with those found in vertebrates reveals many differences. Especially in the degree of change the vertebrates appear in general less plastic and more resistant to inanition, as to environmental influences in general. Thus while many invertebrates may survive a loss of ninety per cent. or more in weight, vertebrates usually perish when the loss reaches forty per cent. Likewise there are found among vertebrates no such radical and profound changes of structure as may occur during inanition among plants and many invertebrates, especially in those which undergo the remarkable process of "reduction."

On the other hand, amidst the diversity of phenomena resulting from inanition in the various plants and invertebrates we find certain features in essential agreement with those occurring among vertebrates, indicating a fundamental resemblance in the reactions of all living organisms. This applies not only to the general atrophy of the whole body, but also to the variable extent and character of change in different parts and organs. Thus the nervous system and (usually) the skeleton are relatively resistant to inanition in both vertebrates and invertebrates. The variable losses in the different parts of the body lead to marked abnormalities of form which differ greatly according to circumstances.

During the development in both animals and plants, inanition (especially of the chronic type) frequently results not merely in a retardation or cessation of growth, but in an abnormal, disproportionate growth, which differs greatly according to the species, stage of development, type of inanition and other factors. Some parts may show persistent growth at the expense of others, even during total inanition with continued loss in body weight. This applies likewise to various types of partial inanition. The abnormal growth occurring in the absence of certain dietary elements necessary for normal nutrition is contrary to Liebig's "law of the minimum or limiting factor" according to which (as narrowly interpreted by some authors) growth should cease when any factor essential for normal growth is exhausted. Whatever may be the influence correlating the relative growth of the various organs and parts this correlation may be markedly changed during total or partial inanition and the process of morphogenesis is accordingly subject to experimental control.

The possibility of regeneration and recuperation upon refeeding after inanition, although more strikingly evident in the lower forms, is characteristic of all living organisms. Although the effects of inanition vary widely in different cases, up to a certain stage of severity perfect recovery is possible; beyond this only partial recovery (or none at all) is possible, resulting in permanently dwarfed and stunted forms. The age at the time of inanition is very important, there being critical periods at which the various organs are most susceptible to change through inanition and other environmental factors. This is strikingly illustrated in the case of the effects upon the sex glands and possibly sex determination.

These various changes observed in the dystrophic organism are associated with changes in the constituent cells. The relative loss in cytoplasm and the resistance of the nucleus during inanition are characteristic in all plants and animals. The general result is to reduce the cell to a more embryonal type of structure with a modified nucleus-plasma ratio, which may perhaps in part explain many of the curious resultant changes in form during dystrophic growth. While mitosis is usually inhibited during inanition, it may persist with great tenacity in those organs in which growth continues.

While the cells during inanition are reduced to an embryonal condition, from which recovery is possible upon refeeding, they do not so remain permanently. Sooner or later, in all living organisms, they pass from a stage of simple atrophy to a condition of degeneration. The cytoplasm typically undergoes cloudy swelling, with subsequent fatty or vacuolar degeneration. The nucleus, though relatively more resistant, also later undergoes progressive degeneration, usually with pycnosis and finally karyorrhexis or karyolysis. It is apparent that the above mentioned possibilities of recovery depend chiefly upon the degree of cell injury which has been sustained. Cells which have undergone extensive cytoplasmic and especially nuclear degeneration are obviously unable to recuperate. There are always great individual differences, however, even among cells of the same organ, so that some may remain capable of regeneration even though others have degenerated beyond the stage of possible recovery.

The question as to why certain cells or organs have a greater resistance to inanition has received various answers. Roux has long held that during inanition those cells persist which require less food in the struggle for existence.

This theory was opposed by Schultz and others who claimed that the order of disappearance of the (invertebrate) organs reverses the order of their appearance during ontogenetic and phylogenetic development. Another view widely held is the teleologic explanation that those organs persist longest which are most valuable to the organism or species. All such theories, however, appear inadequate to explain the facts observed. Runnström (for sea-urchin larvae) proposed a more rational theory, explaining the morphological changes upon the basis of the varying physico-chemical conditions in the starving organism. Future investigation along this line will probably give better comprehension of the phenomena involved.

The question may also be raised as to why the degenerative changes in the various cells during inanition are so similar, not only in the various types of total and partial inanition, but likewise in many other abnormal conditions, such as extremes of temperature, fatigue, toxic or electrical stimuli, etc. Various answers to this question are possible, but the most probable would appear to be that the effects are similar because these all represent conditions which obstruct the normal cell metabolism, thereby causing the same degenerative cell changes. The fundamental similarity in the cellular results of such varied conditions recalls the dictum of Cuénot that "la plupart des influences de milieu se ramènent en somme à des différences de nutrition."

Nutrition therefore becomes a factor of primary importance for morphology as well as for physiology. The form and structure of all living organisms are clearly dependent in large measure upon the quantity and quality of their nutriment. The effects of inanition of various types apparently account for many of the variations observed among living organisms, under both normal and abnormal conditions. A knowledge of these effects gives a deeper insight into the process of morphogenesis and a means whereby it may be experimentally controlled to a degree hitherto generally unrealized. Furthermore, even though it be contrary to the generally accepted biological doctrine, there is another possibility which must be considered. Not only the somatoplasm, but under certain circumstances even the germ plasm may perhaps likewise be modified by nutritional conditions, a possibility of fundamental significance for heredity and evolution.

Clarence M. Jackson

20.9.
1

Reprinted from the PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE,
1922, xx, p. 181

85 (2045)

Organ weights in albino rats with experimental rickets.

By C. M. JACKSON and RACHEL CARLETON.

[*From the Department of Anatomy, University of Minnesota, Minneapolis, Minn.*]

Of the 118 rats used for this work, 37 were normal controls and 81 were young rats which had been fed various diets by Professor McClendon to produce experimental rickets.[1] The 81 test rats were autopsied and classified on the basis of gross skeletal appearance and previous X-ray examination as follows: 27 apparently normal, or nearly so; 19 with slight rickets; 19 with moderate rickets; and 16 with severe rickets. The diagnosis was also confirmed by microscopic examination, although the histological changes were found somewhat variable.

The weights of the various organs and parts were compared with the norms for corresponding body length or weight established by Hatai, Jackson and Donaldson. The percentage deviation was calculated for each organ and averaged for the five groups. The chief results are briefly summarized.

The body weight and tail length appear nearly normal (for corresponding body length) in all. In the rachitic rats the organs may be grouped as follows:

A *decrease* occurs in the weight of the integument, hypophysis, dry skeleton, empty stomach and intestine, and especially in the thymus.

---

[1] PROC. SOC. EXP. BIOL. AND MED., 1922, xix, 356.

An *increase* occurs in the weight of the eyeballs, heart, gastrointestinal contents, and especially in the submaxillary glands, kidneys and suprarenals.

No regular changes of importance were noted in the weight of the head, ligamentous and cartilaginous (moist) skeleton, musculature, brain, lungs, liver, spleen, ovaries, testes and epididymides, although marked variations occur in some groups.

Reprinted from The American Journal of Physiolofy
Vol. 65, No. 1, June, 1923

1010

THE EFFECT OF EXPERIMENTAL RICKETS UPON THE WEIGHTS OF THE VARIOUS ORGANS IN ALBINO RATS

C. M. JACKSON and RACHEL CARLETON

From the Department of Anatomy, University of Minnesota, Minneapolis

Received for publication February 3, 1923

The anatomical lesions in rickets have hitherto been sought chiefly in the skeleton, although an involvement of other organs, especially of the liver, spleen and ductless glands, has often been suspected. Since the effects upon organs are frequently evident by changes in weight, it seems desirable to review systematically the changes during experimental rickets from this point of view.

Material and methods. For the present study, 118 albino rats were used. Of these, 37 are normal controls, 3 to 16 weeks of age, and 22 to 135 grams in body weight. They had been fed chiefly whole-wheat bread and whole milk, supplemented by green vegetables, occasional meat, etc. Out of a large number of rats which had been autopsied (for other purposes) in the Institute of Anatomy, these were selected as controls, corresponding as nearly as possible in body length to the rats used in the present experiments.

The present test rats are 81 in number, ranging from 33 to 147 days of age, and 22 to 132 grams in weight. Most of them are between 2 and 3 months of age and between 30 and 75 grams in body weight, being usually somewhat retarded in comparison with the normal for corresponding age. For these test rats we are indebted to Prof. J. F. McClendon, who had fed them various diets to produce experimental rickets ('22). The experiments usually began when the rats were about one month old. In most cases patent (white) wheat flour formed the basis of the diet, as recommended by Sherman and Pappenheimer ('21), supplemented by casein or lactalbumin, various salt mixtures, and variable amounts of yeast and spinach. In a few cases mixtures of starch, cotton seed oil, casein and lactalbumin replaced the flour. In general, the diets deficient in phosphorus and vitamins (especially A) seemed to be more effective in the production of rickets.

After x-ray examination, the rats were killed by ether or chloroform, and were autopsied in a uniform manner. The general appearance, body weight, body length (nose-anus) and tail length were first recorded. The head was then separated just behind the cranium and in front of the larynx. It was then weighed, the trunk in the meantime being suspended by the tail to drain the blood (unmeasured). Then the various organs were carefully removed, being placed in a moist chamber until weighed, to prevent evaporation. The thyroid gland was not weighed in these rats, but was preserved for histological study. The spinal cord also was weighed in only a few cases, and is not included in the data considered.

Weights for the entire skeleton and the musculature were obtained in some cases as follows. After removal of the integument (which was cleaned of subcutaneous fat and weighed), and of all other organs, together with adherent fat, etc., the skeleton and musculature were weighed together. Then the musculature, including the tendons, was carefully dissected off, leaving the entire skeleton with ligaments intact, so far as possible. This ligamentous skeleton was then weighed, and the weight of the musculature obtained by difference. In some cases, small portions (weighing about 0.1 gram) of the costochondral joints and upper extremity of the tibia were removed for histological study. The ligamentous skeleton was then macerated for about 1 hour in 1 per cent aqueous solution of "Gold dust washing powder," said to contain sodium carbonate, 45 per cent; soap powder, 30 per cent; water 25 per cent (Donaldson and Conrow, '19). The skeletons were macerated at a temperature just below boiling point. The adherent remnants of the ligaments and periosteum were then removed with a small brush, under water, and the remaining cartilaginous skeleton was weighed moist, after removal of the adherent water by filter paper. Finally the cartilaginous skeletons were all dried together for about 3 weeks in open vials in an oven electrically heated to about 95°C., and the dry weight of each skeleton was obtained.

Having thus obtained the weights of the various systems and organs in both test rats and controls, the question of a method of comparison arose. This is always a difficult problem in experimental work of this kind, in which the conclusions are frequently unjustified, on account of insufficient data, inadequate controls and improper methods of comparison. Especially in young animals, the rapid shifts in normal size (relative and absolute) and in structure are likely to make comparisons misleading. In the albino rat we fortunately have a species which has been fairly well standardized for body size and weights of the principal viscera. These have been published in convenient form by Donaldson ('15), together with a good method of comparison for experimental work. The weight of each organ is compared with the norm for corresponding body length (the most satisfactory basis of comparison). The percentage deviation from the norm for each individual organ is then calculated, for both test rats and controls. A comparison of these percentage deviations will indicate whether the apparent changes in the test rats are due to the conditions of the experiment, or are found also in the (presumably normal) controls.

While Donaldson's tables include most of the organs considered, it was necessary to supplement them with data from Jackson and Lowrey ('12) for the weights of the head, integument, musculature and ligamentous skeleton; from Jackson ('13) for the stomach and intestines with contents; from Donaldson and Conrow ('19) for the fresh cartilaginous skeleton; and from Lowrey ('13) for the dry skeleton. In the case of these supplementary data, graphs were drawn for the weight of each organ according to body weight instead of body length (which was not available), and comparisons made as mentioned above. Since in the present experiments the body length remained fairly constant in proportion to the body weight, however, the results of comparison should be very similar, whether body length or body weight is used as the basis.

In order to reveal possible differences in the effects according to the stage or severity of the disorder, the percentage deviations from the norm were averaged in five groups, as shown in tables 1 and 2. These groups were arranged on the basis of the preliminary x-ray examination (especially the thickness of the upper tibial epiphyseal cartilage), and the gross skeletal lesions as follows: *a*, 37 normal controls; *b*, 27 apparently normal, although they had been upon some form of experimental diet; *c*, 19 slightly rachitic (slight costochondral enlargements); 19 moderately rachitic (definite costochondral enlargements, with slight softening and mild deformity of thoracic and limb skeleton); *d*, 16 severely rachitic (marked costochondral enlargements, with pronounced softening and extreme deformity of the skeleton, especially of the thorax and limbs).

TABLE 1

Rats with experimental rickets and controls. Average percentage deviation from norm for organ weights

The corrected data (in parenthesis) for the test rats were obtained by subtracting the average deviation in the corresponding controls.

		TEST RATS ON EXPERIMENTAL DIETS			
	37* normal controls	27* apparently normal	19* slight rickets	19* moderate rickets	16* severe rickets
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Body weight	+ 8.9	+ 9.8(+0.9)	+ 8.3(−0.6)	+12.4(+3.5)	+ 4.6(−4.3)
Tail length	− 5.3	0(+5.3)	− 4.6(−0.7)	+ 3.3(+8.6)	+ 4.4(+9.7)
Head weight	− 2.5	+ 1.9(+4.4)	+ 4.7(+7.2)	+ 8.5(+11.0)	+ 2.5(+5.0)
Integument	−10.0	− 2.2(+7.8)	−30.0(−20.0)	−24.1(−14.1)	−22.1(−12.1)
Lig. skeleton	−13.2	+ 5.9(+19.1)	−13.2(0)	+ 1.8(+15.0)	+ 2.6(+15.8)
Cart. skeleton	+24.3	+ 3.8(−20.5)	+22.6(−1.7)	+21.0(−3.3)	+17.0(−7.3)
Cart. skeleton (dry)		+27.3	− 7.3	−19.1	−18.5
Musculature	+ 4.4	+ 7.4(+3.0)	+ 3.2(−1.2)	− 3.4(−7.8)	− 7.8(−12.2)
Submaxillary glands	+43.3	+21.9(−21.4)	+58.3(+15.0)	+95.2(+51.9)	+92.3(+49.0)
Brain	+ 1.8	− 2.1(−3.9)	− 2.3(−4.1)	− 1.1(−2.9)	− 2.6(−4.4)
Eyeballs	+14.5	+15.5(+1.0)	+19.6(+5.1)	+28.8(+14.3)	+40.6(+26.1)
Thymus	+ 3.4	−30.1(−33.5)	−33.3(−36.7)	−52.8(−56.2)	−66.5(−69.9)
Heart	+ 8.7	+23.5(+14.8)	+17.1(+8.4)	+28.8(+20.1)	+26.3(+17.6)
Lungs	+ 7.9	+13.4(+5.5)	− 0(−7.9)	+16.8(+7.9)	+ 6.1(−1.8)
Liver	−22.0	− 2.1(+20.9)	+14.1(+36.1)	− 8.9(+13.1)	−27.7(−5.7)
Spleen	+53.2	+13.7(−39.5)	+27.7(−25.5)	+61.9(+8.7)	+37.7(−15.5)
Stomach—intestines (empty)	−25.0	−43.0(−18.0)	−34.0(−9.0)	− 7.7(+17.3)	−48.7(−23.7)
Stomach—intestines (+ contents)	− 0.1	+12.9(+13.0)	+33.4(+33.5)	+14.7(+14.8)	+25.6(+25.7)
Suprarenals	− 2.3	+42.4(+44.7)	+42.0(+44.3)	+45.8(+48.1)	+62.0(+64.3)
Kidneys	+ 9.5	+42.8(+33.3)	+54.5(+45.0)	+57.6(+48.1)	+51.2(+41.7)
Ovaries	+13.2	+12.5(−0.7)	+36.8(+23.6)	+41.3(+28.1)	+ 4.7(−8.5)
Testes	+15.8	+55.8(+40.0)	− 1.7(−17.5)	+ 4.0(−11.8)	+21.2(+5.4)
Epididymides	+11.8	+35.1(+23.3)	+ 5.4(−6.4)	+44.1(+32.3)	+30.6(+18.8)
Hypophysis	+15.8	−10.9(−26.7)	−12.2(−28.0)	− 8.4(−24.2)	− 1.4(−17.2)

* In the case of the integument, skeleton, musculature, empty stomach-intestines, submaxillary glands and gonads, the number of observations is considerably less, as explained in the text.

On account of individual variations, there was naturally difficulty in grouping some of the cases, but the final result probably represents approximately the degree of severity of the rachitic lesions. Since the diagnosis of rickets is always uncertain upon the basis of gross appearances alone, microscopic examination of the stained sections (from material with or without decalcification) was made, which corroborated the diagnosis. Although there are marked variations in histological structure, the characteristic osteoid tissue and other irregularities

TABLE 2

Cartilaginous skeleton of rats with experimental rickets. Individual data

RAT NUMBER	AGE	BODY WEIGHT	MOIST CARTILAGE SKELETON	DRY CARTILAGINOUS SKELETON		
				Weight	Per cent of fresh cartilaginous skeleton	Compared with norm
			Apparently normal rats			
	days	*grams*	*grams**	*grams*	*per cent*	*per cent*
25.1	63	70	6.9	2.657	38.5	+ 6
25.2	67	75	6.8(+0.1)	2.978	43.8	+10
25.3	65	91	8.1	3.704	45.7	+14
25.4	65	86	8.9(+0.1)	3.706	41.6	+24
25.5	63	93	9.0	4.485	49.8	+37
25.6	68	64	7.1(+0.1)	3.657	51.5	+66
27.1	61	71	8.1	3.347	41.2	+34
			Slight rickets			
27.3	61	74	6.2	1.974	31.8	−24
28.2	86	90	8.7	3.622	41.6	+13
29.3	72	66	6.5(+0.1)	2.045	31.5	−11
			Moderate rickets			
27.4	58	72	6.4	1.392	21.8	−44
28.1	84	84	8.0	2.393	29.9	−20
29.1	70	71	6.8(+0.1)	2.654	39.0	+ 6
			Severe rickets			
27.5	58	59	5.0	1.603	32.1	−20
29.2	73	71	6.5(+0.1)	2.069	31.8	−17

* In some cases the weights do not include a small piece removed for histological examination (indicated in parenthesis).

occur in the rachitic skeleton, corresponding in general to the recent descriptions by Pappenheimer, McCollum, Park, Shipley and their co-workers, using similar methods.

Unfortunately the weights for all of the organs were not secured in all cases. Thus complete data for the skeleton were available in only 15 test rats, as shown in table 2. Other organs in which the number of observations is incomplete are as follows:

ORGANS	NUMBER OF OBSERVATIONS IN			
	Apparently normal	Slight rickets	Moderate rickets	Severe rickets
Integument	16	9	14	11
Musculature	9	4	7	5
Submaxillary glands	24	13	8	7
Empty stomach and intestines	6	3	4	1
Ovaries	10	5	7	2
Testes	15	9	9	8
Epididymides	14	5	6	5

For the other organs the data are complete, or nearly so, in each case. Even in these organs, however, the numbers in each group are too small to justify a statistical analysis which is highly desirable. The normal variation in the weights of the organs in the rat was studied by Jackson ('13). The present data allow merely a preliminary study, and the results are to be regarded as suggestive rather than conclusive.

Observations (table 1): *Body weight.* The body weight (compared with the norm for corresponding body length) averages for all groups slightly above the norm. The normal controls themselves apparently average 8.9 per cent above the norm, and if this figure is subtracted from the data for each test group, as indicated in parenthesis, it is seen that the body weight is apparently nearly normal in relation to body length. To a certain extent, however, this appearance is deceptive, since an increase in the intestinal contents (as will be shown later) masks a certain amount of loss in body weight in the test rats.

The *tail length* likewise shows no marked change in the test rats, although there is an evident tendency to relative elongation in the groups with moderate and severe rickets.

The *head weight* appears slightly above normal in all the test groups, but the increase is small and of doubtful significance, especially in the severely rachitic group.

The *integument* in the "normal controls" averages 10 per cent below the norm for body length. In the test groups (excepting the "apparently normal"), the integument is still more subnormal in weight, though not progressively so, varying from 20 per cent below in the slightly rachitic to 12 per cent below in the severely rachitic. The decreased weight is possibly due to loss in fat.

Skeleton. The averages for the various groups are shown in table 1. In view of the small number of observations and the marked individual variations, as shown in table 2, conclusions must be correspondingly guarded.

The *ligamentous skeleton* in the test groups shows no significant deviation in weight from the norm for corresponding body length. Since the "normal controls" average 13 per cent below the norm, however, the corrected data for the test rats appear correspondingly higher. But this apparent increase occurs also in the "apparently normal" test group, and is of somewhat doubtful significance.

The moist *cartilaginous skeleton* appears considerably above the norm in the rachitic groups; but this is also true for the "normal controls." These apparent differences are probably due to a difference in technique by which the skeletons for the norm were prepared (by Donaldson and Conrow). It is therefore doubtful whether there is any significant change in the weights of the moist cartilaginous skeleton. The individual data are given in table 2.

For the *dry cartilaginous skeleton,* however, the results are quite different. No data for the dry skeleton were available in the "normal control" group. In the "apparently normal" test group, the dry skeleton averaged 27 per cent above the norm. In the slightly rachitic rats it averaged 7 per cent below the norm, and in the moderately and severely rachitic about 19 per cent below. The marked individual variation is shown in table 2. Thus the weight of the dry skeleton in the "apparently normal" group ranged from 6 to 66 per cent above norm; in the slightly rachitic from 13 per cent above to 24 below; in the moderately rachitic from 6 per cent above to 44 below; and in the two severely rachitic 17 and 20 per cent below the norm. Since the moist skeleton is usually nearly normal in weight, these data for the dry substance indicate an extremely variable deficit in dry substance (especially in calcareous material).

The data for the *musculature* indicate a slight but progressive loss in weight for the three rachitic groups, amounting to about 12 per cent subnormal in the severely rachitic.

The *submaxillary glands* appear markedly (43 per cent) above norm in the "normal controls," possibly due to the inclusion of associated lymph nodes. Even deducting this figure from the averages for the test groups, however, there remains an apparent increase of 15 per cent in the slightly rachitic, 52 per cent in the moderately rachitic and 49 per cent in the severely rachitic groups.

The *brain* is remarkably uniform in weight in all groups, with very slight individual variability. It appears below the norm in all the test groups; but the difference is very slight (less than 5 per cent, even in the corrected groups), and shows no progressive change, so it is of doubtful significance.

The *eyeballs*, on the other hand, appear above the norm in all groups. Even when the 14.5 per cent excess for the "normal control" group is deducted, the corrected data for the test groups show a progressive increase up to 26 per cent above for the severely rachitic group.

The *thymus* averages slightly above the norm in the "normal control" group, but shows a progressive decrease in the test groups, reaching about 70 per cent subnormal weight in the severely rachitic group. This may appear remarkable when it is recalled that the body weight-length ratio is nearly normal, but on the other hand nearly all of the test rats were subnormal in weight according to age, indicating a retardation in growth.

The *heart* weight averages above the norm in all groups, even slightly (8.7 per cent) in the "normal controls." Deducting this figure gives corrected data indicating a hypertrophy in the test groups, even in the "apparently normal," but most marked (18 to 20 per cent) in the moderately and severely rachitic.

The *lungs* show some irregularities in weight, but apparently no significant deviation from the norm.

The *liver* appears irregular in weight. Even the "normal controls" average 22 per cent below the norm. (Donaldson's norm based upon Hatai's data is probably somewhat high.) When the data for the test groups are correspondingly corrected, it would appear that the liver is above normal in weight in the earlier stages, 21 per cent above in the "apparently normal" and 36 per cent in the slightly rachitic; decreasing to 13 per cent above normal in the moderately rachitic and 6 per cent subnormal in the severely rachitic.

The *spleen* is an organ notably variable even in normal weight. In our "normal control" group it averages 53 per cent above Donaldson's norm (which appears too low, because the largest spleens were excluded in Hatai's data upon which this norm is based). Deducting this figure to obtain the corrected data for the test groups, the spleen averages about 40 per cent subnormal in the "apparently normal" group, 26 per cent subnormal in the slightly rachitic, 9 per cent above normal in the moderately rachitic and 16 per cent subnormal in the severely rachitic. These figures are so irregular that their significance is very doubtful.

The *empty stomach and intestines* appear below the norm in weight in all groups, even in the "normal controls" (−25 per cent). In the corrected data, the test groups still appear subnormal, excepting the moderately rachitic, which averages 17 per cent above. The data for the empty canal are somewhat inconclusive, on account of both the scanty data and the difficulty in obtaining a uniform technique; but on the whole they appear to indicate a tendency to subnormal weight in the rachitic rats.

In the *stomach and intestine with contents*, on the other hand, there is a marked increase in weight, averaging 13 per cent above normal in the "apparently normal" group, and 15 to 34 per cent in the rachitic groups. Since the empty canal is usually subnormal in weight, the increase is clearly due to excessive contents. The distention of the intestines with liquid as well as gas is often strikingly apparent in the rachitic rats. In extreme cases, the intestinal contents may equal 20 per cent or more of the body weight, which (as above mentioned) introduces a possible error of considerable importance in interpreting the gross body weight. Normally, the intestinal contents usually form less than 10 per cent of the gross body weight.

The *suprarenal glands* appear nearly normal (−2.3 per cent) in weight in the "normal control" group, but are markedly above normal in the test groups. The increase appears slightly progressive in character, the (corrected) weights appearing 45 per cent above in the "apparently normal" group, 44 per cent in the slightly rachitic, 48 per cent in the moderately rachitic, and 64 per cent in the severely rachitic group. Although there is a sex difference in the weights of the suprarenal glands (larger in the female rat), an examination showed the increased weight to be similar in both sexes, so the data are not separated in the table.

The *kidneys* average slightly (9.5 per cent) above the norm in the "normal control" group, but very much more in the test groups. The corrected data indicate a weight 33 per cent above for the "apparently normal" group, 45 per cent for the slightly rachitic, 48 per cent for the moderately rachitic and 42 per cent for the severely rachitic. The increase is therefore fairly progressive for the various stages, excepting the last.

The *ovaries* (corrected data) appear considerably above normal in the slightly and moderately rachitic groups, but slightly subnormal in the severely rachitic. The *testes* also appear irregular, their deviations tending to be opposite to those for the ovary in corresponding groups. The *epididymides* apparently tend to hypertrophy in the moderately and severely rachitic groups (32 and 19 per cent above normal). On account of the small number of observations and the great physiological variability in the weights of the gonads, however, no definite conclusions can be drawn from these data.

The *hypophysis*, however, shows a fairly uniform tendency to subnormal weight. This affects both sexes, although they are not separated in the tabulation of the results. The "normal controls" averaged 16 per cent above the norm. The test rats (corrected data) show an average of 27 to 28 per cent subnormal in the "apparently normal" and slightly rachitic groups, but less marked (24 and 17 per cent subnormal) in the moderately and severely rachitic groups. The subnormality therefore appears greatest in the earlier stages.

Discussion. Although the literature on rickets is enormous, we find very little quantitative data for comparison with the present findings. For human rickets, the frequent enlargement of the liver and (especially) the spleen was noted by Whistler (1645) and by many subsequent observers; but the significance of this hypertrophy has been much disputed, according to reviews of the earlier literature by von Starck ('96) and Sasuchin ('00). Stoeltzner ('03) could find no significant visceral changes in rickets, with the possible exception of hydrocephalus. Vincent ('04) states that the lesions involve not only the bones, "but also implicate the brain, liver, spleen, muscles, and, indeed, every organ may be affected to a greater or less extent." The enlarged head is said to be due to thickening of the cranial bones, the facial skeleton being arrested in growth. The muscles are poorly developed. The spleen is moderately enlarged in the progressive stage, but not permanently. The liver is less frequently and less markedly enlarged.

Cheadle and Poynton ('07) agree that in human rickets the enlargement of the head is due chiefly to cranial thickening, the capacity being normal (except in hydrocephalus). The muscles are wasted; the liver usually normal in size, rarely enlarged; the spleen also sometimes enlarged. The skin may appear normal, except for anemia; the subcutaneous fat is variable, sometimes abundant, sometimes scanty. The heart appears variable, but probably shares in the general malnutrition.

Stoeltzner ('04, '08) claimed that the suprarenal glands are atrophied in rickets, but this was not confirmed by Cattaneo ('05). Stoeltzner ('09) also supports the theory of a specific regressive dystrophy of the musculature in rickets, including an atrophy of the smooth muscle in the intestinal wall (which results in meteorism). The frequent enlargement of the spleen is not considered essential. The thymus was found hypertrophied by du Castel ('08) and by Marfan ('22). Lehnerdt ('10) concluded (p. 134) that "Bei Rachitis ist die Knochengewebemasse als ganzes in der Regel nicht vermindert, sondern in ähnlichen Mengen vorhanden wie in der Norm, meist ist sie sogar in erheblichem Masse vermehrt."

In experimental rickets, E. Voit ('80) compared the organ weights of a normal puppy (body weight 4510 grams) with another of the same age and litter, which appeared markedly rachitic after a calcium-poor diet of extracted meat plus lard and distilled water (body weight 4710 grams). Voit's table of absolute and relative weights shows no significant difference between the two puppies in the weights of the skin, adipose tissue, muscles, bones (fresh), cartilage, brain, spinal cord, and empty stomach-intestine. The following organs appear larger in the test dog than in the control, as indicated (in parenthesis) by the percentage of the body weight formed by each organ in test and control, respectively: lungs (0.97–0.89 per cent); liver (5.45–4.74 per cent); heart (0.83–0.77 per cent); genito-urinary organs (kidneys and bladder?) (1.24–1.01 per cent); pancreas, spleen and thymus (1.07–0.42 per cent). The increases are thus relatively small, except for the last group (unfortunately weighed together). The weights of the dry skeleton indicate a loss in the rachitic puppy, with a water content of 71.9 per cent in comparison with 64.9 per cent in the control.

Dibbelt ('09) gives weights of several organs in 5 puppies, one normal and 4 rachitic (on calcium-poor diet of horse-meat and starch). Unfortunately only one of the test puppies (no. VI, 4995 grams) is near enough in weight to the control (no. IV, 6000 grams) to make even rough comparison possible. Relative to body weight, there is in these two cases apparently no significant difference in the weight of the brain, spleen and kidneys. The heart is absolutely as well as relatively larger in the rachitic puppy, weighing 43 grams, while only 39 grams in the larger control. The same is true for the moist humerus (28.5 grams in test puppy, 23.9 grams in the control); the dry humerus, however, weighs 13.0 grams in the rachitic, 9.8 grams in the control. The lungs appear atrophic in the rachitic puppy, weighing 35.5 grams, in comparison with 72.0 grams in the control; likewise the liver (116.5 to 203 grams).

In the more recent work on experimental rickets in rats by methods similar to those used in the present study, Shipley, Park, McCollum and Simmonds ('21) note incidentally that the spleen is found atrophic in some rats, more or less enlarged in others. The thymus is atrophic. McCollum, Simmonds, Shipley and Park ('21) state that in rachitic rats the spleen is frequently greatly enlarged, the thymus and gonads atrophic. McCollum, Simmonds, Kinney, Shipley and Park ('22) find the thymus atrophied in the rachitic rats. The spleen is enlarged in some cases, but usually not above normal.

Comparing our results with the foregoing, we may conclude that our findings as to the skeletal weights, fresh and dry, are in substantial agreement with the statements of previous observers in both human and experimental rickets. Likewise as to the atrophy of the thymus (excepting du Castel and Marfan), and the irregularity of the spleen. Like Cattaneo, we fail to confirm Stoeltzner's claim of a suprarenal atrophy in rickets, finding a hypertrophy instead. Although there is a slight tendency to agreement, we fail to find in the rats a pronounced atrophy of the musculature or a marked increase in the size of the head, both of which are considered characteristic for human rickets. Our observation of a cardiac hypertrophy in the rat agrees with Voit and Dibbelt for rachitic puppies, but has not been noted in human rickets. Similarly a hypertrophy of the kidneys, as found in our rats, appears also in Dibbelt's puppy, but not in Voit's. The integument appears variable in human and canine rickets, with no definite tendency to atrophy as found in our rats. The lungs were slightly irregular in weight with little change in our rats; in puppies, Voit found a slight apparent increase, but Dibbelt a decrease in weight. The liver also appears variable in weight, both in human and in animal rickets. As in our brain weights for the rat, no significant difference appears in the data of Voit and Dibbelt for rachitic puppies. Our data do not confirm the atrophy of the gonads found in rachitic rats by McCollum, Simmonds, Shipley and Park. No data for comparison were found concerning the weights of the hypophysis, stomach and intestines, eyeballs and submaxillary glands.

In interpreting the results of the present experiments, we must remember that even where the changes are unquestionably significant it does not necessarily follow that they are essential to rickets. They may be due to variations in the diet which have little or nothing to do with the production of the characteristic rachitic lesions. This may explain some of the marked changes in certain organ weights of the "apparently normal" group. Similarly in human rickets some of the changes may be due to "complications." On the other hand, it is equally possible that some of these early changes in experimental rickets are due to the rachitic factors, which might cause unsuspected changes in organ weights before the typical rachitic lesions appear. Some of the changes, however, such as atrophy of the thymus and hypertrophy of the suprarenals, occur also during inanition and other nutritional disorders. Further investigation is therefore necessary before the significance of the changes in organ weight during experimental rickets can be interpreted.

SUMMARY

We may group the various organs and parts of the body, according to apparent changes in weight during experimental rickets in our rats, into 3 groups. The first group shows a definite decrease in weight. This group includes the integument, hypophysis, dry skeleton, empty stomach and intestines, and especially the thymus. The average decrease is regularly progressive in the case of the thymus and dry skeleton, although marked individual variations occur.

The second group, which shows an increase in weight, includes the eyeballs, heart, gastro-intestinal contents, and especially the submaxillary glands, kidneys and suprarenal glands. The average change appears fairly progressive in all except the heart and gastro-intestinal contents.

The third group includes those in which the apparent changes are slight or irregular. This group includes the head, ligamentous and (moist) cartilaginous skeleton, musculature, brain, lungs, liver, spleen, ovaries, testes and epididymides. The head, however, shows a slight tendency to increase and the musculature to decrease in weight. The liver averages above normal in the earlier stages, decreasing later. The gonads and spleen are very irregular in weight, the latter usually subnormal.

Only very scanty and indefinite data for comparison are found in the literature, but our findings appear to be in general agreement with those of previous observers on human and animal rickets as to the weights of some organs, including the fresh and dry skeletal weights, thymus (in rats), spleen, heart, liver, lungs and brain. To some extent this applies also to the head and musculature, but for other organs our results are in disagreement with those of previous workers, or there are no data available for comparison.

Great caution is necessary in interpreting these changes in organ weights, even where the changes are unquestionably significant, as they may be due to factors other than those essential to the production of rickets.

BIBLIOGRAPHY

du Castel: C. R. Soc. Biol., Paris, 1908, lxv, 725.

Cattaneo: V. Kongr. d. italien. Ges. f. Kinderh., 1905, Rome (cited by Funk, The vitamines, 1922).

Cheadle and Poynton: Rickets; in Allbutt's System of medicine, 1907, iii, 78.

Dibbelt: Arb. a. d. path. Inst. Tübingen, 1909, vii, 144.

Donaldson: The rat; Memoirs of the Wistar Inst., no. 6, 1915, Philadelphia.

Donaldson and Conrow: Amer. Journ. Anat., 1919, xxvi, 237.

Jackson: Amer. Journ. Anat., 1913, xv, 1.

Jackson and Lowrey: Anat. Rec., 1912, vi, 449.

Lehnerdt: Ergebn. d. inn. Med. u. Kinderheilk., 1910, vi, 120.

Lowrey: Anat. Rec., 1913, vii, 143.

Marfan: Paris Méd., 1922, xii, 409 (Abstr. in Journ. Amer. Med. Assoc., 1922, lxxix, 2255).

McClendon: This Journal, 1922, lxi, 373; Proc. Soc. Exper. and Biol., 1922, xix, 412; ibid., 1922, xix, 356.

McCollum, Simmonds, Kinney, Shipley and Park: Amer. Journ. Hyg., 1922, ii, 97.

McCollum, Simmonds, Shipley and Park: Amer. Journ. Hyg., 1921, i, 492.

Sasuchin: Jahrb. f. Kinderheilk., 1900, li, 297.

Sherman and Pappenheimer: Journ. Exper. Med., 1921, xxxiv, 189.

Shipley, Park, McCollum and Simmonds: Johns Hopkins Hosp. Bull., 1921, xxxii, 160.

von Starck: Deutsch. Arch. f. klin. Med., 1896, lvii, 265.

Stoeltzner: Charité-Annalen, 1903. (Abstr. in Monatschr. f. Kinderheilk. 1904, ii, 149.)

Stoeltzner: Pathologie und Therapie der Rachitis, Berlin, 1904.

Stoeltzner: Med. Klinik, 1908; also Centralbl. f. allg. Path. etc., 1909, Erg. z. Bd. xx (Verh. d. deut. path. Ges., xiii, 20).

Vincent: The nutrition of the infant, 2nd ed., London, 1904.

Voit: Zeitschr. f. Biol., 1880, xvi, 55.

Whistler, De morbo puerili anglorum, 1645, London (cited by v. Stark, 1896).

Loll.

AUTHOR'S ABSTRACT OF THIS PAPER ISSUED
BY THE BIBLIOGRAPHIC SERVICE, MAY 28

FURTHER CONTRIBUTIONS TO THE STUDY OF THE EVOLUTION OF THE FOREBRAIN[1]

J. B. JOHNSTON

Anatomical Laboratory, University of Minnesota

ONE HUNDRED AND TWO FIGURES

CONTENTS

1. The corpus striatum.......... 338
    a. Nucleus caudatus and stria terminalis.......... 339
    b. Putamen.......... 357
    c. Globus pallidus.......... 364
2. The tuberculum olfactorium, diagonal band and anterior perforate space.. 369
3. Composition of the stria terminalis.......... 381
4. The amygdaloid complex.......... 397
    a. General. The amygdaloid fissure.......... 397
    b. The amygdala of the opossum.......... 409
    c. The amygdala of mammals.......... 420
    d. Summary of the amygdala.......... 456
Summary of results.......... 475

In several earlier papers the writer has dealt with the general morphology of the forebrain, the structure of the telencephalon in fishes and reptiles and the history of the hippocampus in all classes of vertebrates. Further studies pursued at irregular intervals during the past six years have aimed to trace the evolution of the basal portions of the cerebral hemispheres, the corpus striatum, amygdaloid complex, tuberculum olfactorium, anterior perforate space, lobus pyriformis and related structures. Attention has been given also to such general problems as the primary relations of the forebrain to the primitive functional columns of the brain stem; the significance of the forebrain in the morphology and evolution of the vertebrate head; the processes involved in the evagination and enlargement of the cerebral hemisphere and in the formation of its poles, especially the temporal pole; and the earliest recognizable beginnings of the olfactory and the general pallium and the determining factor in their differentiation and development. The point of view from which this work proceeds is that the structural and functional relationships in the adult brain of man or higher animals are to be understood in the light of the evolution of structure in the brain of ancestral forms under the influence of environment and adaptive behavior or habits.

---

[1] Neurological studies from the University of Minnesota, no. 24, July 25, 1922.

I desire to express my thanks to Dr. Richard Scammon for the loan of his collection of selachian embryos and to Dr. C. E. Johnson for the loan of embryos of Chelydra serpentina.

1. THE CORPUS STRIATUM

The corpus striatum consists of several nuclei and is traversed by important fiber bundles. The globus pallidus is a somewhat conical mass of cells situated deep in the crus, the apex of the cone being turned in the direction of the thalamus. This nucleus is of ancient origin, being recognizable at least in the more primitive reptiles. The putamen is an extensive mass of cells lateral to the globus pallidus, laterally flattened and often much elongated. It is pierced in various ways by bundles of the internal capsule and is bounded externally by the external capsule, outside of which lie the claustrum, the capsula extrema and the insular cortex. The caudate nucleus lies internal to the putamen, occupying the floor of the ventricle and forming a semicircular band of gray matter curving about the internal capsule and extending from the region of the olfactory nuclei in front to the amygdaloid region behind. Closely parallel with the medial border of the caudate is a strand of fibers, the stria terminalis, which relates various olfactory nuclei in front with the amygdaloid nuclei behind.

The following description will show that the stria terminalis in the human embryo and in all lower vertebrates is accompanied by a prominent mass of gray matter which is continuous rostrally with the olfactory nuclei and caudally with component nuclei of the amygdaloid complex, and that the stria terminalis therefore represents an important primary element of forebrain structure. It and its related gray masses form part of the primitive olfactory apparatus. It is older than the caudate nucleus which overshadows it in the human brain.

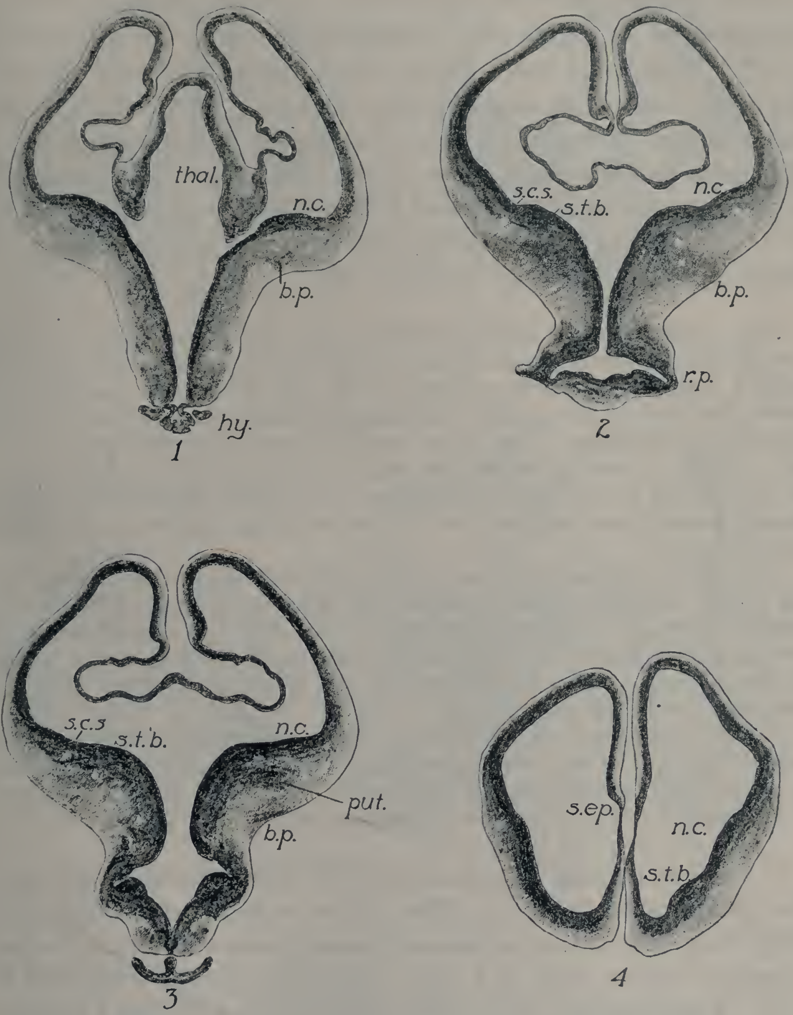
a. Nucleus caudatus and stria terminalis

Human embryos. When either serial sections or dissections of the brains of human embryos or foetuses are studied the most striking fact seen in the lateral ventricle is that its floor is formed of two prominent parallel longitudinal ridges. These occupy the place commonly assigned in descriptive anatomy to the corpus striatum, or more specifically to the caudate nucleus. These two ridges appear in the accompanying figures showing sections of the hemispheres in various stages from an embryo of 18 mm. crown-rump length to a foetus of the eighth month. The more medial of these two ridges imbeds the stria terminalis (figs. 1 to 16). The more lateral ridge is closely related to the lateral border of the general pallium in early stages. This is

ABBREVIATIONS

a.b., basal area in the selachian brain
acc., nucleus accumbens
a.l., ansa lenticularis
alv., alveus
am., amygdala
a.o.l., undifferentiated lateral olfactory area
a.p., area parolfactoria
a.p.a., area perforata anterior
b., basal amygdaloid nucleus
b.acc., accessory basal amygdaloid nucleus
b.l., lateral part of basal amygdaloid nucleus
b.o., bulbus olfactorius
b.p., basal proliferation in human and reptilian embryos
c., central amygdaloid nucleus
c.a., commissura anterior
c.c., corpus callosum
c.d., cortex dorsalis
c.e., capsula externa
c.f., columna fornicis
c.g.l., corpus geniculatum laterale
c.h., commissura hippocampi
c.i., capsula interna
ch., chiasma opticum
cl., claustrum
c.l., cortex lateralis
c.m., corpus mammillare
cort., cortical amygdaloid nucleus
c.r., corona radiata
crus, crus cerebri or lateral forebrain bundle
c.s., commissura superior
c.st., corpus striatum
d.b., diagonal band of Broca
di., diencephalon
d.v.r., dorsal ventricular ridge
f., fornix

f.am., fissura amygdalæ
fasc.m., fasciculus marginalis
f.chor., fissura chorioidea
fi., fimbria
f.p., fissura prima
f.pc., fasciculus præcommissuralis
f.d., fascia dentata
f.o., formatio olfactoria
for.d., foramen interventriculare
fov., fovea isthmi
f.rh., fissura rhinalis
gl.p., globus pallidus
g.p., general pallium
g.s., gyrus subcallosus
h., hippocampal formation
hab., nucleus habenulæ
hy., hypophysis
hyth., hypothalamus
i.C., islands of Calleja
l., lateral amygdaloid nucleus
l.b., longitudinal association system of the amygdala and pyriform lobe
l.pyr., lobus pyriformis
l.t., lamina terminalis
m., medial amygdaloid nucleus
m.f.b., medial forebrain bundle
n.c., nucleus caudatus
n.d.b., nucleus of the diagonal band
n.l., nucleus lentiformis
n.m., nodulus marginalis
n.o., nervus olfactorius
n.o.a., nucleus olfactorius anterior
n.p.l., nucleus parolfactorius lateralis
n.p.m., nucleus parolfactorius medialis
n.t., nervus terminalis
n.t.o.l., nucleus of the lateral olfactory tract
nuc.am.m., medial amygdaloid nucleus
nuc.am.b., basal amygdaloid nucleus
nuc.am.b.acc., accessory basal amygdaloid nucleus
nuc.am.bas.m., medial part of basal amygdaloid nucleus
nuc.am.bas.l., lateral part of basal amygdaloid nucleus
nuc.am.c., central amygdaloid nucleus
nuc.am.cort., cortical amygdaloid nucleus
nuc.am.l., lateral amygdaloid nucleus
olf.proj., olfactory projection tract
p., preoptic region
pa.th., pallial thickening
p.c.f., precommissural fiber system
p.h., primordium hippocampi
p.o., pedunculus olfactorius
pul., pulvinar
put., putamen
s.c.s., strio-caudate sulcus
s.en., sulcus endorhinalis
s.ep., septum ependymale
s.f.d., sulcus fimbrio-dentatus
s.l., sulcus limitans hippocampi
s.l. H., sulcus limitans of His
s.m., stria medullaris
s.rh., sulcus rhinalis
s.t., stria terminalis
s.t.b., bed of stria terminalis
s.t. 1,2,3,4,5, bundles of the stria terminalis described on p. 382
sub., subiculum cornu ammonis
s.v.d., dorsal ventricular sulcus
s.v.m., middle ventricular sulcus = strio-caudate sulcus
thal., thalamus
thal.rad., thalamic radiations
t.o., tuberculum olfactorium
tr.d.b., tract of diagonal band
tr.olf., tractus olfactorius
tr.o.l., lateral olfactory tract
tr.o.m., medial olfactory tract
tr.op., tractus opticus
v.l., ventriculus lateralis
v.o., groove leading to the olfactory ventricle
v.t.o., ventricle of the tuberculum olfactorium
x, fiber system crossing the diagonal band obliquely perhaps from lobus pyriformis to hypothalamus
z, bundle from amygdala to tuberculum olfactorium
z.l.l., zona limitans lateralis
z.l.m., zona limitans medialis
1,2,3,4,5, see s.t. 1, 2, 3, 4, 5
III,IV, nuclei of the third and fourth nerves



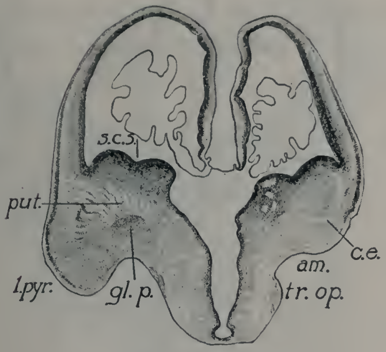
Figs. 1, 2, 3, 4 Four transverse sections of the telencephalon of a human embryo of 18 mm. C.R. H. 260 Minn. Anat. × 15.

The bed of the stria and the caudate ridge extend from the region of the temporal pole to that of the olfactory peduncle. Figures 1, 2, and 3 show a proliferation of cells (*b.p.*) medio-ventral to the stria bed which is concerned in the formation of the tuberculum olfactorium, anterior perforate space, diagonal band and perhaps part of the amygdaloid complex. Figure 3 shows an additional proliferation (*put.*) which is probably related to the future lentiform nucleus.

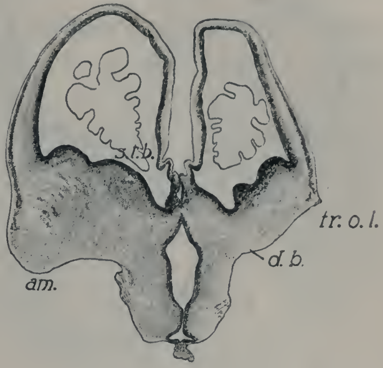
directly comparable with the dorsal ventricular ridge of turtles, development of which was described six years ago (Johnston, '16 b). This ridge forms in the adult the greater part of what has been known as the caudate nucleus. This origin of the caudate and its homology with the dorsal ventricular ridge of the turtle and the significance of the bed of the stria terminalis were presented in a paper read before the American Association of Anatomists in 1917, of which the following abstract was published in The Anatomical Record ('18).

> The caudate nucleus consists of two parts, ventral and dorsal, which are distinct in structure and origin and in functional relations. The ventral portion is closely related to the olfactory and parolfactory nuclei, the bed of the anterior commissure and the medial part of the amygdaloid complex. The dorsal portion forms the chief part of the ridge which in man is called the 'tail' of the caudate nucleus. It is closely related to the lentiform nucleus, especially behind the internal capsule where these two enter into a common mass lateral to the amygdaloid complex.
>
> The ventral portion is a part of the olfactory apparatus throughout the vertebrate series. The dorsal portion becomes prominent first in the reptiles where it forms the dorsal ventricular ridge. Its development in reptiles and mammals shows that it is derived from the lateral border of the pallium. The dorsal portion has fiber connections with the internal capsule and the pallium.
>
> The stria terminalis is a complex bundle connecting the rostral and caudal parts of the olfactory apparatus. It and the gray mass in which it is imbedded (ventral portion of caudate) have been greatly elongated in mammals on account of the increased volume of the internal capsule.

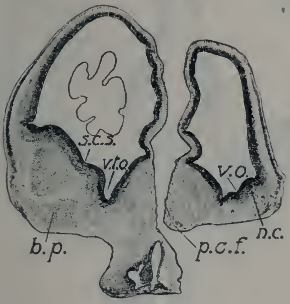
In an illuminating discussion in 1919, Elliot Smith emphasizes the derivation of the body which I have called dorsal ventricular ridge from the cortex in Sphenodon and points out that he had observed this in 1897 and made reference to it in 1902 and in 1910. The statement in the latter place (Arris and Gale Lectures) is very brief and is not accompanied by figures or description so that its significance was not clear to the present writer. Professor Smith states ('19, p. 288): "One fact in connection with this discussion I did not appreciate until a few months ago. The hypopallium of reptiles persists in the mammalian brain where it forms the greater part of the caudate nucleus and of the putamen of the lenticular nucleus, the globus pallidus repre-



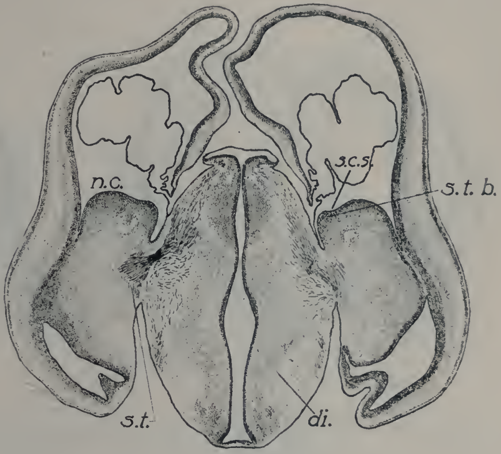
5



6



7



8

Figs. 5, 6, 7 Transverse sections of the telencephalon of a human embryo of 26 mm. C.R. H. 21 Minn. Anat. × 7.5.

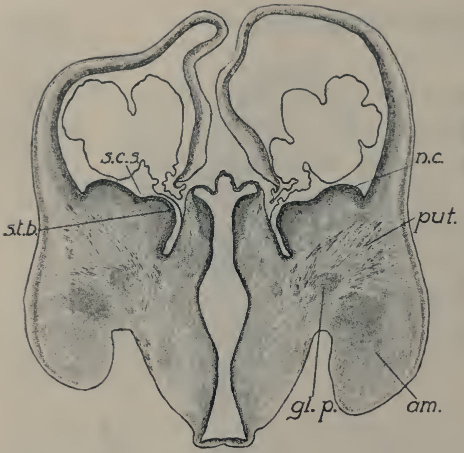
Fig. 5 Through the temporal pole. The two ventricular ridges, the internal and external capsules, the pyriform lobe, amygdala and globus pallidus can be recognized.

Fig. 6 Through the bed of the anterior commissure. The bed of the stria on the left side contributes to the commissure bed.

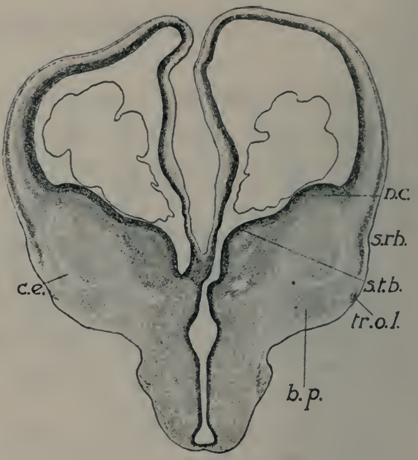
Fig. 7 In front of the anterior commissure. On the right side appear the diagonal band fibers (*p.c.f.*), on the left the ventricle of the tuberculum olfactorium.

Figs. 8 to 16 Transverse sections of the telencephalon of a human embryo of 33 mm. C.R. H. 16 Minn. Anat. × 7.5.

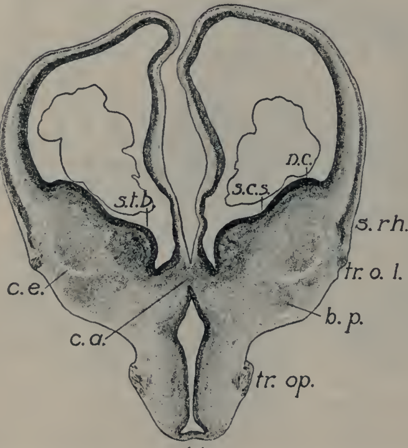
Fig. 8 Through the caudal border of the internal capsule where the stria terminalis curves around it. The stria bed and caudate ridge are separated by a shallow groove, the strio-caudate sulcus.



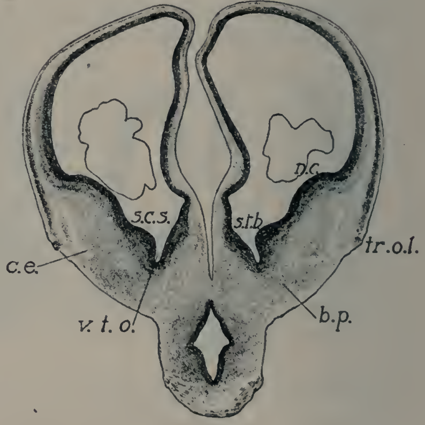
9



10



11



12

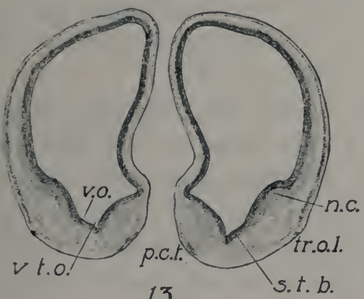
Fig. 9 Through the middle of the crus and the anterior part of the thalamus Note the globus pallidus deeply imbedded in the crus.

Fig. 10 Just behind the anterior commissure. Note the collection of cells in the region of the anterior perforate space and the diagonal band. As in H. 260 these cells are continuous forward with the anlage of the tuberculum olfactorium (fig. 12).

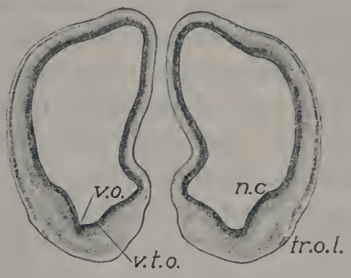
Fig. 11 Through the anterior commissure bed. Note that the bed is continuous at either side with the bed of the stria terminalis. The putamen is identified in the last section and this by its position in the concavity of the external capsule.

Fig. 12 At the caudal border of the tuberculum olfactorium showing its ventricle. The basal proliferation is forming a cortex covering the region of this ventricular pouch just as the tuberculum does in selachians and generally in vertebrates.

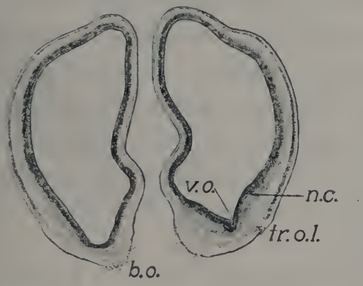
senting the major portion of the palaeostriatum. In the development of the mammalian brain the phylogenetic history of the corpus striatum is clearly revealed." These homologies will be



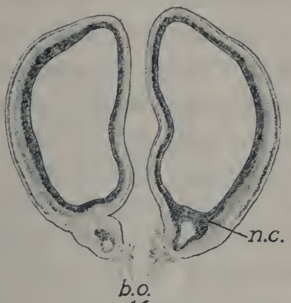
13



14



15



16

Fig. 13 At the rostral border of the precommissural fiber system. Note that the stria bed is shifting toward the medial wall, tending to obliterate the ventricle of the tuberculum. From here forward the strio-caudate sulcus (labeled *v.o.* in this figure) leads into the ventricle of the olfactory bulb.

Fig. 14 Just behind the olfactory peduncle. The stria bed has passed into the medial wall. The strio-caudate sulcus descends in the next few sections into the olfactory ventricle.

Fig. 15 At the base of the olfactory peduncle.

Fig. 16 Through the olfactory bulb. The caudate ridge enters into the dorsal wall of the peduncle.

examined further on. It appears that the present writer's announcement in 1918 gave the first indication of the homology of the caudate nucleus of mammals with the dorsal ventricular ridge of reptiles.

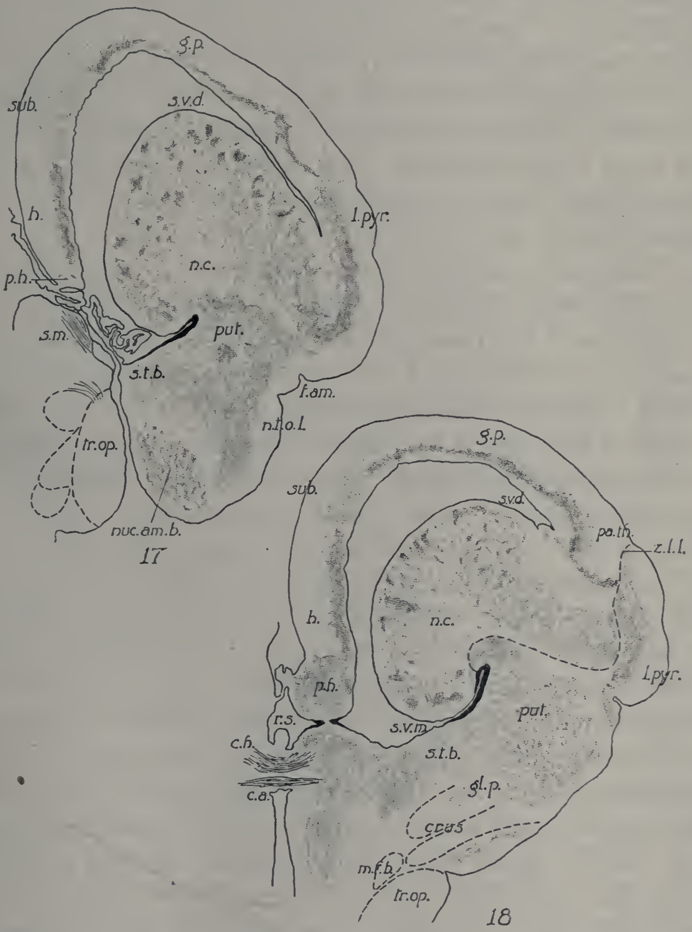
The two ridges mentioned above have been seen by Miss Hines ('22) who has called them medial and lateral corpus striatum.

In mammals the groove separating these two ridges may be called the striocaudate sulcus. It is homologous with the middle ventricular sulcus in the turtle brain (figs. 17, 18).

The bed of the stria terminalis in human embryos extends from the temporal pole forward to the base of the olfactory peduncle (figs. 1 to 16). It is very interesting to note that the stria bed bends into the medial wall just in front of the ventricular pouch of the tuberculum olfactorium and beneath the olfactory peduncle, while the caudate ridge joins the middle wall above and in front of the peduncle forming its dorsal wall (figs. 14, 15, 16). It is the strio-caudate sulcus and not the ventricle of the tuberculum olfactorium which leads into the ventricle of the olfactory bulb. At the level of the future anterior commissure in embryos of 26 and 33 mm. the ridges of the two sides are enlarged and the cell-masses approach the median plane to form the bridge of tissue through which the fibers of the anterior commissure afterwards run (figs. 6, 11). At this level in the adult the fibers of the several constituent bundles of the stria terminalis take various courses to be described later.

The rostral continuation of the ridge gives rise to a mass of cells the relations and nomenclature of which require some explanation. In the basal wall of the forebrain just behind the bulbar formation in reptiles and mammals there is a mass of cells functioning as a secondary olfactory nucleus. This is included in a region variously named by older authors olfactory area, posterior olfactory area, and postolfactory lobe or nuclei. Herrick in 1910 used the term nucleus olfactorius anterior to designate extensive undifferentiated tissue of secondary olfactory function in amphibia, lying between the bulbar formation and the differentiated nuclei of the forebrain. The writer ('13b, '15b) has applied the same term to the above mentioned restricted area in the basal wall in reptiles and mammals. The location of the corresponding restricted center in amphibia is shown in figures 44 to 47. It is seen also in figures 11 (*em. po.*) and 29 of

Herrick's 1910 paper. Miss Crosby figures it in the alligator in the ventral wall below the primordium hippocampi. Whatever may be the significance of the more extensive tissue which Herrick has called the nucleus olfactorius anterior, it should be



Figs. 17, 18 Two transverse sections of the telencephalon of the turtle Cistudo carolina, corresponding to figures 15 and 18 of a previous paper ('15 b), redrawn and lettered in accordance with the interpretations given in the present paper. *s.v.m.* is the same as the strio-caudate sulcus in mammals. The letters *gl.p.* stand in the place from which the photograph shown in figure 80 was taken. Note especially the position of the zona limitans lateralis as explained in a previous paper ('16 b, p. 489).

noted that the term as used in this paper applies only to the more limited and better defined body in the basal wall.

As this anterior olfactory nucleus is followed caudad in sections of reptilian or mammalian brains it comes to be divided by a depression of the floor of the ventricle. This horn of the ventricle dips down into the tuberculum olfactorium and the anterior olfactory nucleus is divided by it into two limbs, a medial which lies in the ventro-medial brain wall (wrongly called septum by most authors) and a lateral limb usually assigned in mammals to the head of the caudate. The division of the one continuous mass into two limbs is particularly well shown in the turtle (Johnston, '15 b, figs. 23 to 28, *a.p.* and *n.c.*, and *n.o.a.*). This whole V-shaped mass forms the deep gray of which the tuberculum olfactorium with its islands of Calleja forms the cortex. The medial limb has been called by Kappers ('08) nucleus accumbens septi and by Herrick ('10, '21) sometimes nucleus accumbens septi and sometimes nucleus lateralis septi. It lies in the ventricular part of the medial wall and is covered medially (ectally) by the 'nucleus medianus septi,' also a secondary olfactory nucleus. In an earlier paper ('13 b) I have shown reason for abandoning the use of the term septum for this region and have used for these two nuclei the names nucleus parolfactorius lateralis and medialis respectively. The use of the term septum in the names of these nuclei implies that this region is homologous with the septum pellucidum of mammals, which is not the case. It has nothing whatever to do with the structure properly called septum in man or mammals. The terms area parolfactoria and nucleus parolfactorius carry no misleading implications and their use would remove much of the confusion which exists regarding this region. In the latest paper from Professor Herrick's laboratory (Hines, '22) the term septum is transferred wholly from the septum pellucidum of human embryos or the homologous region in other animals to the region called by the present writer the parolfactory area.

Kappers and his associates contend that the nucleus accumbens belongs to the striatum and that it has invaded the medial wall secondarily. Whether the presence of one limb of this olfactory center in the medial wall is due to a secondary invasion or merely to a sort of folding and lateral compression which has produced the tuberculum with its horn of the ventricle is immaterial. The nucleus accumbens is more closely related with a portion of the 'striatum' than with the structures in the medial wall, but the purpose of this discussion is to show that this portion of the striatum must be recognized as an olfactory center and clearly distinguished from the rest of the striatum. The use of the term lateral parolfactory nucleus is no longer necessary. This nucleus should be regarded as a unit with the bed of the stria.

In mammals with large olfactory apparatus this gray mass is large and its lateral limb forms a large part of the head of the caudate nucleus. The relations in this region are illustrated in numerous figures in my paper on the septum, hippocampus and pallial commissures ('13 b, figs. 27, 41, 50, 66, 67, 68) and in figures 60, 61, 63, 64, 79, 90 and 93 of this paper. In all cases that portion of the head of the caudate which rests in the concavity of the tuberculum olfactorium is a secondary olfactory nucleus continuous rostrally with the nucleus olfactorius anterior and caudally with the band or ridge of gray matter lying medial to the caudate nucleus and forming the bed of the stria terminalis and of the anterior commissure as well. Heretofore the writer has accepted the statement of Elliot Smith that the bed of the anterior commissure is formed from the paraterminal body, and the paraterminal body is essentially an olfactory center occupying the ventro-medial wall of the hemisphere. In human embryos, however, it is clear that the cells which form the bed of the anterior commissure proliferate from the ventricular cell layer of the medial of the two ridges in the floor of the lateral ventricle and migrate to the median plane to form the bridge through which the fibers afterward cross. In the turtle also the same process appears to take place. This is shown in figures 48 and 49 from an embryo of Chelydra serpentina. While it is true that the anterior commissure crosses through the paraterminal body, the cells which form its immediate bed migrate in from the lateral wall. These cells come indeed from the deep or ventricular portion of the lateral olfactory area, from which arise some of the most fundamental and constant fibers of the commissure. This only means that cells from the lateral olfactory center migrate into the medial center (paraterminal body) to form the bed for decussating fibers which were primarily related to the lateral area.

A more detailed description will show clearly the existence of an important gray mass in human embryos running parallel with and medial to the nucleus caudatus and having intimate relations with the anterior olfactory centers.

In human foetuses older than those above referred to, the cell material of the two ridges in the floor of the ventricle has undergone differentiation so that one distinguishes masses of true nerve cells and a ventricular layer which stains deeply because of its closely packed cells. This ventricular layer doubtless contains, in addition to the bodies of ependyma cells, many germinal cells which are destined to become neuroblasts or glia cells. It is enormously thicker than the adult ependyma. This ventricular layer is everywhere divided into two areas corresponding to the two ridges seen in younger embryos. The sulcus separating these areas (*s.c.s.*, figs. 57, 60, 88, 89, 90, 92) is sometimes very broad and shallow and sometimes not recognizable, but everywhere the ventricular layer itself presents differences of structure. Both parts are well supplied with blood vessels and capillaries. These are more numerous in the medial portion which overlies the stria terminalis and they have a peculiar or distinctive mode of branching. These differences are shown in figures 88 and 89.

Beneath the ventricular layer in the lateral ridge in all specimens up to the eighth month, appears the gray mass overlying the internal capsule which is known as the caudate nucleus. In many places this mass is continuous with the putamen through spaces between the fascicles of the internal capsule. Beneath the medial ridge lies the stria terminalis imbedded in a mass of gray which varies in volume and density at different levels. In the region of the anterior commissure there is a considerable mass of gray in which the bundles of the stria terminalis are diverging to their several destinations. This is shown in figure 88 for a foetus of 175 mm.

Forward from this level the bed of the stria terminalis continues on as a considerable mass next to the ventro-medial angle of the ventricle while the caudate proper is lateral to it (figs. 82, 89, 90, 93). This medial part of the head of the caudate is continuous with the nucleus accumbens and the nucleus olfactorius anterior. The relations of this gray of the stria terminalis are well shown also in sagittal sections of the brain of a foetus of 200 mm. C. R. length (fig. 91). The section passes through the olfactory bulb and peduncle, the central gray of which is seen in continuity with the gray surrounding the lateral ventricle. Immediately behind the peduncle is the olfactory tubercle whose peculiar structure extends far dorsally, and behind this is the diagonal band of Broca. Above the tuberculum is the caudate and behind that the ventricular layer of the bed of the stria terminalis. From this layer peculiar dense cords of cells reach down both in front of and behind the tuberculum to the base of the olfactory peduncle. These cell cords are conspicuous in all the foetal brains studied. They are seen in figures 82, 89, 90. The cords behind the anterior commissure also are connected with the bed of the stria terminalis.

Behind the anterior commissure the bed of the stria is massive for a short distance but over and behind the internal capsule it is reduced to a narrow band which remains clearly distinct back to the amygdaloid complex.

Behind the internal capsule where the bundles of the stria diverge to be distributed to the several amygdaloid nuclei the gray matter accompanying them expands into the large central nucleus and the medial nucleus of the amygdaloid complex. These structures and the behavior of the stria will be more fully described in section IV.

Mammals, reptiles, fishes. This mass which forms the bed of the stria terminalis and anterior commissure may be readily recognized in the mammals and in lower orders of vertebrates. In the rhesus monkey there is evidence of gray matter accompanying the stria terminalis throughout its length and this enlarges greatly in the amygdaloid complex and in the olfactory region (figs. 40, 41, 42, 43).

In the rabbit occasional nerve cells are scattered along the course of the stria terminalis and as the bundle approaches the amygdaloid complex, gray matter appears more abundantly between its fibers and this expands into the large medial and central nuclei. Rostrally cells appear in small masses somewhat behind the bed of the anterior commissure with which these masses fuse. Horizontal sections through the anterior commissure show admirably the continuity of the bed of the stria terminalis with that of the commissure and with the nucleus parolfactorius lateralis and the nucleus olfactorius anterior (figs. 63, 64, 65).

The rat possesses a prominent mass of gray lying over and behind the anterior commissure which might almost be called a special nucleus of the stria terminalis (fig. 19). It consists of a dense collection of cells near the point of contact of the stria medullaris and fornix columns, which is continuous with that mass of gray matter which passes down behind the anterior commissure and follows the fornix column toward the hypothalamus. A short distance behind this point, the gray matter accompanying the stria is reduced to a mere vestige as in other forms. Going forward from the anterior commissure the bed of the stria very clearly continues forward and downward over the medial surface of the anterior limb of the commissure to join the medial part of the head of the caudate and the nucleus accumbens.

In the bat (Myotis) for some distance dorso-caudal to its point of contact with the anterior commissure the stria terminalis is imbedded in a large gray mass, much larger relative to the size of the brain than in any other form studied. Then where the stria passes over the internal capsule and is pressed upon by the fimbria it is slender but still accompanied by cells. The stria expands into the medial nucleus of the amygdala as in other forms described.

In the opossum the very large size of the anterior commissure makes the paraterminal body seem relatively small. The stria terminalis has nerve cells interspersed among its fibers throughout its whole course (figs. 54, 57, 58), and in some places these appear both in Weigert and cell preparations as small masses of gray matter. At the rostral end the bed of the stria terminalis fuses with the bed of the anterior commissure, which is completely encircled by the fibers of the stria, and continues forward to the nucleus olfactorius anterior as above described. Caudally the

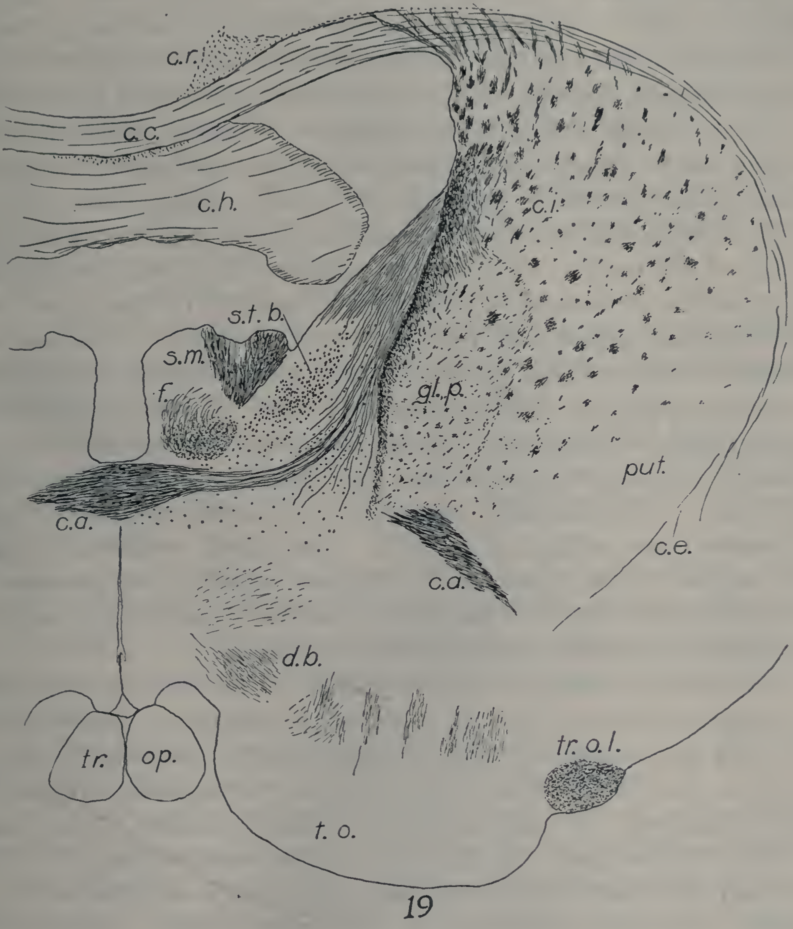


Fig. 19 A transverse section of the brain of the white rat at the caudal border of the anterior commissure. The figure shows the large nucleus in the stria bed above the commissure and the continuity of the stria bed with the bed of the anterior commissure and the gray descending behind the commissure toward the hypothalamus. Note also the internal capsule bundles scattered throughout the caudate nucleus and putamen.

stria bed expands directly into the medial and central amygdaloid nuclei to which some of the stria bundles are distributed. Other bundles pass into other nuclei, but there is a break of continuity seen in cell preparations, and in Weigert sections these nuclei are separated from the bed of the stria by well defined layers of fibers. Thus in the opossum there is a continuous band or column of gray matter from the nucleus olfactorius anterior to the amygdala, through which run the fibers of the stria terminalis.

In the turtle the stria terminalis is a broad diffuse bundle which lies in a large gray area forming the ventro-lateral wall of the lateral ventricle, beneath the middle ventricular groove. This area was called 'nucleus caudatus' in my paper on the forebrain of the turtle ('15 b) and was labeled *n.c.* in all the figures. Two of the sections shown in figures 15 and 18 of that paper are redrawn and reproduced here as figures 17 and 18. The reader should compare these figures in order to understand clearly the new interpretation which is presented here. It was not until the embryology of the dorsal ventricular ridge was studied ('16 b) that the writer recognized the true homologue of the caudate nucleus. A preliminary statement of the interpretation here presented was published in 1918. The dorsal ventricular ridge of reptiles forms most of the nucleus caudatus of mammals, while the structure now called stria bed forms part of the head of the caudate and the bed of the stria terminalis.

To clearly identify the homologue of the bed of the stria terminalis in fishes it is only necessary to compare a cross-section of a human embryo through the region of the tuberculum olfactorium (figs. 7, 12) with a section in the corresponding region of the embryonic or adult selachian brain (Johnston, '11 a, figs. 17, 18, or Holmgren, '22, fig. 21). In the human embryo there is a sharp depression of the ventricle which forms as above noted a pouch especially related to the olfactory tubercle. The same thing exists in the selachian brain. The tuberculum is much more extensive in the selachian than in the mammal but in both its lateral border comes into contact or continuity with the lateral olfactory area (gray accompanying the lateral olfactory tract, anterior part of lobus pyriformis of Elliot Smith). On the ventricular surface, the structure which lies lateral to the ventricular pouch of the tuberculum in the selachian certainly corresponds topographically to the bed of the stria terminalis in the human embryo. This area in the selachian is a secondary olfactory center and corresponds to the lateral olfactory nucleus and the lateral part of the tuberculum on the external surface. For all practical purposes it is proper to regard this area as the ventricular aspect of the lateral olfactory nucleus. This area extends in the selachian forebrain throughout the length of the lateral olfactory nucleus. No distinct stria terminalis has been described in it but if it contains any association fibers connecting anterior olfactory nuclei with the caudal part of the lateral nucleus, such fibers would constitute a stria terminalis.

From this description it appears that—

1. The stria terminalis is imbedded in a mass of gray which primarily connected the anterior olfactory area with the region in which the amygdaloid complex develops.
2. This gray mass occupies the ventricular part of the ventrolateral wall of the lateral ventricle in the selachian and may be regarded generally as the ventricular or deep portion of the lateral olfactory area.
3. The stria terminalis includes a commissural bundle for the nuclei of the lateral olfactory tracts, and fibers connecting the amygdaloid complex with the parolfactory nuclei and the hypothalamus. (A more complete analysis and description is given below.)
4. The bed of the stria terminalis includes part of what is known in human anatomy as the head of the caudate.
5. The caudate (exclusive of that part related to the stria terminalis) does not appear in fishes but first makes its appearance in the primitive reptiles as a prominent ridge projecting into the dorsal part of the lateral ventricle from the lateral wall. In the turtles this ridge has nothing whatever to do either with the nucleus accumbens or with the mass in the lateral wall with which the nucleus accumbens is related. The latter mass is the bed of the stria terminalis and is separated from the caudate ridge by a deep ventricular groove. In mammals the two bodies come

together in such a way that the bed of the stria terminalis forms most of what is called head of the caudate and the new ridge forms the rest of the head and the tail of the caudate.

6. The dorsal ventricular ridge of reptiles receives fibers from the internal capsule and is pierced by others on their way to the general pallium. In these respects it corresponds to the greater part of the caudate nucleus.

7. This ridge arises in both turtles and mammals by an infolding or hypertrophy of the lateral margin of the general pallium.

8. The locus of this infolding is along the lateral border of the general pallium. The line of infolding is marked by the rhinal fissure which marks the dorsal or lateral boundary of the lobus pyriformis.

9. The adjacent pallium in the turtle is the excitable pallium or motor area (Johnston, '16 a).

Professor Smith calls attention ('19, p. 289) to the constancy of the position and relations of the lateral striate arteries as evidence in corroboration of the homologies suggested by him. The lateral striate arteries enter the brain along the line of the endorhinal fissure latero-caudal to the tuberculum olfactorium in reptiles and mammals, and supply the corpus striatum including the caudate nucleus. The position of these vessels would support beautifully the hypothesis that the caudate nucleus was invaginated along the line of the endorhinal fissure, the supposition being that the vessels had entered the brain along the line of infolding. The beauty of this illustration, however, is spoiled by two facts: *a* that in the turtle many important vessels enter the caudate nucleus (dorsal ventricular ridge) through the middle of the area pyriformis and through the rhinal fissure dorsal to the area pyriformis, and, *b* that the caudate nucleus is not invaginated along the line of the endorhinal fissure but from the border of the general pallium along the line of the rhinal fissure. I gave considerable time to the study of these arteries in 1912 and 1913, thinking that they ought to throw light on these very questions. All I can see is that most of the arteries which supply the caudate nucleus in reptiles and mammals enter the brain through the endorhinal fissure. These seem to be expansions of arteries which enter the brain along the same fissure in fishes. Only those arteries which enter the caudate nucleus along the rhinal fissure seem to have followed the course of immigration of pallial elements and so would lend corroboration to the observations concerning the derivation of the caudate nucleus from the pallium.

The contribution of Shellshear ('20) does not give any account of the arteries which enter the caudate nucleus in reptiles through the area pyriformis or in the rhinal fissure.

No change in the customary nomenclature is required to embody the interpretation here presented. In the B N A the nucleus caudatus and stria terminalis are recognized as independent structures. It is only necessary now to recognize that the stria terminalis is imbedded in an independent mass of gray matter and that anteriorly this stria bed includes gray which has been assigned to the head of the caudate. When Elliot Smith ('19, figs. 18, 19, 20) speaks of the lower part of the nucleus caudatus being 'palaeostriatal,' I suppose it is this gray bed of the stria terminalis to which he refers.

b. Putamen

The relations of this lateral portion of the nucleus lentiformis require careful study in human embryos and in lower mammals in order to make sure of its homologue in lower orders of vertebrates.

In the brain of a human foetus of the eighth month this nucleus is a broad plate of gray thickest near its rostral border where it is covered by the anterior bundles of the internal capsule and the head of the caudate. Its extreme rostro-ventral angle is seen in a coronal section passing through the tuberculum olfactorium and the anterior perforate space. Posteriorly and dorsally it is bounded by the posterior limb of the corona radiata passing into the pallium. On the ectal surface it is covered by the external capsule, claustrum and pallium of the insula. Internally or medially the putamen is bounded by the anterior commissure, the globus pallidus and the posterior limb of the internal capsule. The lower border of the putamen is deeply notched where the anterior commissure passes beneath it to reach the external capsule in which the temporal branch of the commissure runs back. The portion of the putamen behind this notch is much smaller than the portion in front of it. The anterior portion of the putamen continues on forward and downward in contact with the anterior limb of the internal capsule, the deep lateral gray of the olfactory tubercle and certain scattered but large and important gray masses related to the diagonal band of Broca. These masses push back following the anterior commissure and laterad between the commissure and the anterior part of the putamen into contact with the external capsule beneath the insular pallium. The posterior portion of the putamen remains separated from the amygdaloid complex by the posterior border of the internal capsule. Along the medial surface of the anterior commissure bundle the putamen comes into contact with the most caudally placed masses of cells belonging to the diagonal band (figs. 95, 96). At the extreme temporal angle of the putamen it becomes broken up or subdivided by the bundles of the internal capsule and enters into connection with the enlarged tail of the caudate by thick bands of cells passing between these bundles.

In younger foetal brains the putamen bears essentially the same relations. In the 145 mm. foetus the putamen comes into closer relations with the amygdaloid complex and with the tuberculum olfactorium than in the eight-month foetus. In this younger foetus the putamen extends forward beyond the base of the olfactory peduncle. In all the foetal brains the appearances strongly suggest that the internal capsule bundles do not pass between two essentially distinct and independent nerve centers, the caudate and the putamen, but that these two are rather one continuous body which is pierced by the bundles of the internal capsule. Throughout the whole width of the internal capsule the compact bundles composing it leave spaces between them which are filled by cords or bands of cells which fuse indistinguishably with the caudate above and the putamen below. There is no conspicuous difference in the size, appearance or arrangement of the cells above and immediately below the internal capsule.

This appearance of essential continuity and similarity of the caudate and putamen suggests study of their embryological origin and their relations in lower animals. In human embryos the caudate and putamen can both be clearly recognized at least as early as the stage of 26 mm. (fig. 6). At this stage the external capsule is already clearly formed and the representative of the putamen lies just within or medial to it. The next younger embryo available which is well preserved is 18 mm. in length. Four sections from this are shown in figures 1, 2, 3, 4. The external capsule is not developed but the internal capsule and crus are to be seen. Beneath the internal capsule (figs. 1, 2, 3) appears a dense proliferation of cells from the ventro-lateral angle of the ventricular wall which goes to form the tuberculum olfactorium and extends far back toward or into what will be the temporal pole (p. 369). Above the internal capsule and between it and the two ventricular ridges (stria bed and caudate) is another dense cell mass which may represent the globus pallidus. It is surrounded by an extensive area of cells less compactly arranged. Proliferation of cells is going on from both the ventricular ridges, and from the pallium cells seem to be migrating down to the basal or striatal area. The future putamen is doubtless present in this diffuse cell area but this embryo does not show its origin with any certainty. In an embryo of 13 mm. the two ventricular ridges are slightly marked. There is a continuous band of proliferated cells outside both ridges and cells are coming from both ridges and from the border of the pallium.

From the human material at my disposal I am inclined to believe that the lentiform nucleus is laid down by the earliest proliferation of cells in the lateral wall of the hemispheres (before the 13-mm. stage) and that it may receive later additions by cells migrating from the lateral border of the pallium and possibly from the caudate ridge.

If these surmises are true, there is a significant resemblance between the caudate nucleus and the putamen to the extent that the latter is derived from the lateral part of the primary general pallium. There is a distinct difference in that the putamen seems to be formed chiefly from an earlier proliferation of cells, even before the ridge which gives rise to the caudate nucleus can be recognized.

It is worth while to examine the relations and structure of the putamen in lower mammals and a marsupial. In sections of the rabbit brain stained with neutral red which show the general disposition of medulated tracts and demonstrate admirably the size, form and arrangement of the nerve cells, together with their chromatin content, I can see no clear distinction in structure between the caudate and the putamen. Both consist of small cells diffusely scattered without regular arrangement and of larger, more deeply stained cells which are also unevenly scattered through both nuclei. Many bands of cells connect the two bodies through the internal capsule and the two are continuous at the caudal end near the amygdala. In one respect the putamen of the rabbit differs markedly from that of the human foetus: the anterior commissure passes beneath the anterior border of the putamen to reach the external capsule in which it turns caudad, so that the part of the putamen behind the anterior commissure is much larger than it is in man.

The rat has an unusually diffuse arrangement of the internal capsule bundles (fig. 19). The bundles spread through the whole corpus striatum to reach the corona radiata. The largest and most closely packed bundles rise up through the internal part of the corpus striatum near the ventricle. Here, where one looks for the caudate nucleus as an area of gray matter free from large internal capsule bundles, there is no gray free from fibers, but instead the largest bundles. There is no line of demarcation between caudate and putamen, but the globus pallidus is vaguely indicated by the arrangement of fiber bundles.

In sections of the brain of the bat (Myotis) stained with a cell stain (neutral red) one can speak only of a common or combined caudate-putamen. There is no difference in the appearance or arrangement of the cells throughout the area and there is no separation into two bodies or masses. The internal capsule passes through the common gray mass in many bundles diverging like the rays of a fan. Farther caudally, at the level where the stria terminalis turns ventrad around the caudal surface of the internal capsule, the caudate-putamen appears as a somewhat comma-shaped mass bounded laterally by the relatively very large lateral nucleus of the amygdaloid complex and the pallium; and medially by the ventricle and the expanding bed of the stria terminalis adjacent to the medial and central amygdaloid nuclei (fig. 77). Forward from the anterior commissure again there is only a large common mass bounded by the external capsule laterally and containing flattened bundles of the internal capsule.

Cell preparations of the brain of the opossum show the caudate nucleus and putamen at the level of the anterior commissure to hold very much the same relations as in the bat (figs. 57, 58). There is no distinction as to size or arrangement of cells and the internal capsule is divided into many bundles between which the gray matter is continuous. The internal capsule has a smooth and regular outline toward the caudate and is denser on that side, while toward the putamen it is broken up into several larger and smaller bundles. It appears as if the internal capsule traverses the putamen rather than the caudate nucleus. Forward from this level the putamen rapidly diminishes so that at the rostral border of the anterior commissure (fig. 59) it is only a small area through which the more lateral bundles of the internal capsule rise to the pallium. Behind the anterior commissure (figs. 57, 58) the putamen is larger for a time and is bounded medially by the internal capsule and the globus pallidus. Farther back the putamen grows smaller, becomes wedged in between the central and lateral nuclei of the amygdaloid complex and at the same time fuses with the tail of the caudate nucleus.

In Weigert preparations many small fascicles are seen turning up from the internal capsule to spread out in the caudate nucleus. The same is true of the putamen, although it is not so conspicuous because of the large bundles which pass directly through it. The fiber arrangement gives a distinctive appearance to the lower and caudal part of the putamen adjacent to the globus pallidus.

In turtle embryos as previously described (Johnston, '16 b, '18) at the same time that the dorsal ventricular ridge, the homologue of the caudate, makes its appearance, there is formed quite independently and ventro-lateral to it an active proliferation of cells which gives rise to the homologue of the putamen. In examining the figures of the 1916 paper the reader should understand the reference letters as follows: *n.c.*, bed of stria terminalis; *n.l.*, putamen; *d.v.r.*, caudate nucleus. The caudate nucleus and the putamen both grow rapidly during the stages which I have studied and form two clearly distinct structures in the adult as described in 1915 b.

In the adult turtle the fibers of the internal capsule on their way to the pallium run through the putamen and not through the caudate ('15 b, figs. 32, 33). This is much more striking than it is in the opossum. Fibers of the internal capsule also end in both nuclei, those for the caudate emerging from the general course of the bundles going to the pallium. Behind the internal capsule the putamen loses its identity through fusion with the caudate nucleus, as in all mammals studied. Thus, in the turtles as in the mammals, both the putamen and the caudate nucleus establish their functional relations through afferent and efferent fibers of the internal capsule and therefore belong to the somatic mechanisms. At the same time it is clear that the two nuclei have quite distinct origins in the embryo and remain distinct in the adult except at their caudal ends. It is perhaps not surprising that two bodies so closely related in function should become less distinct in the mammalian series.

The caudate nucleus is formed for the first time in vertebrate phylogeny in primitive reptiles by an infolding of the border of the general pallium or by a migration of cells inward from this region. The putamen is an older structure, which can be recognized in the brain of fishes. In selachians, as the writer has described earlier ('11 a), the lateral forebrain bundle contains well defined ascending and descending fibres comparable with the thalamic radiations of mammals. General sensory and optic radiations were described. These fibers enter an area of gray matter lying in the lateral wall of the telencephalon medium to which the name somatic area was given. At that time it was assumed that the sensory fibers ended in that area and that the descending fibers took origin from the large cells of the same area. From this area arises a large bundle of fibers which runs upward and forward to cross in the roof above the hippocampal commissure. This was believed to be the primitive corpus callosum. Later it was seen that the cells of the somatic area continue up into the roof along the course of the commissure. This was recorded in my note book in December, 1914, as follows: Two specimens of Scyllium canicula "show clearly that a considerable mass of cells accompanies the corpus callosum and the olfacto-somatic association tract upward and forward from the somatic area to a point well over the olfactory peduncle. This prolongation of the somatic area is traversed by the fibers mentioned and is quite distinct from the lateral olfactory area. It passes up (into the roof) caudo-dorsal to the olfactory area." In a third specimen "the band of somatic cells seems to turn toward the mid-line at its anterior end" and in a fourth specimen, "it looks as if the forward prolongation of the somatic area is already somewhat distinct and perhaps forms a dorsal pallium, while the somatic area represents the corpus striatum." Lacking fresh material for study and being crowded by other duties, I could only surmise that this elongated somatic area which received ascending thalamic radiations and gave rise to descending fibers and to an independent dorsal forebrain commissure represented the common material for the development of both general pallium and the corpus striatum. It was upon this basis that figures 59 and 60 of the paper 1915 b were published. This surmise is now confirmed by the admirable studies of Professor Holmgren ('22) on embryonic and young specimens of Acanthias. He shows clearly the presence of both hippocampal formation and general pallium in the roof of the forebrain and explains that they have become relatively obscure in the adult owing to the compact form which the forebrain takes on. Whatever conclusions we are to draw regarding the history of the general pallium—it seems clear that the body in the lateral wall of the telencephalon medium of selachians through which thalamic radiations pass forward must correspond at least roughly to the lentiform nucleus of reptiles and mammals. In truth, it is scarcely appropriate to speak of a corpus striatum in reptiles, so widely separated are the two main parts which enter into the compact 'basal ganglion' of mammals and man. Here in the selachian there is no sign of the differentiation of the future nucleus caudatus but the assumption is that it is represented in the lowly organized, dorsal general pallium, from which it is derived in the reptiles. This would leave the body in the lateral wall of the telencephalon of selachians to be interpreted as either putamen or putamen plus globus pallidus. The following discussion of the globus pallidus will lead us to include it in this undifferentiated somatic area in the selachian.

c. *Globus pallidus*

It is not necessary to describe the relations of the globus pallidus in man or typical mammals. The characteristics which are most important for comparative study are the large size of its cells and its close association with the deep part of the internal capsule. While the upper (inner) bundles of the capsule are compact and pass over the globus pallidus, the lower (outer) bundles are infiltrated with cells which constitute the globus center. These cells are conspicuously larger than those of the putamen and in my neutral red preparations usually take a deep stain of a purple hue. Figures 66 and 30 to 35 show the fiber arrangement in the rabbit and the opossum respectively. In the human foetus there is a clear distinction between the outer and inner portions of the globus pallidus. In the outer portion the fibers of the internal capsule are less compact and there are large nerve cells scattered irregularly, together with a large number of glia cells. This portion is pale compared with the putamen with its closely packed nerve cells and occasional fiber bundles. The inner portion is much more pale because of the compactness of the deep part of the internal capsule and because the glia elements are much less numerous. The large nerve cells are at least as numerous as in the outer portion and there are occasional dense clumps or clusters of them.

In the rabbit there is not so clearly marked a distinction between the inner and outer portions, but they can be recognized. The outer portion is marked by longitudinal fibers interlaced with the bundles of the internal capsule. The cells are disposed with their long axes parallel with these longitudinal fibers. Most of the cells of the globus pallidus are of about the same size as the large cells in the putamen above mentioned. In addition there are present a considerable number of cells of much larger size. These are found in both outer and inner portions but are most numerous along the margin of the globus next the putamen and there is an especially large collection of such cells near the caudo-lateral angle of the globus (fig. 66). At the rostro-ventral border of the internal capsule the cells of the globus are scattered among the fiber bundles and bring the globus pallidus into close relation with the preoptic region. The basal portion of the globus really follows the crus down into the thalamus. Anteriorly there is a large elongated collection of large globus cells medio-caudal to the temporal limb of the anterior commissure (fig. 67) which is directed toward the gray of the diagonal band, but never comes into contact with the latter. Following horizontal sections from above downward, as the diagonal band spreads toward the temporal pole to reach the amygdaloid complex the globus pallidus recedes and remains in close relation with the crus. Its most basal portion is closely applied to the optic radiations and extends medially along the anterior border of the crus into continuity with the gray of the hypothalamus. Finally, the large globus pallidus cells continue in large numbers along the optic radiations to the caudal border of the internal capsule where the putamen and nucleus caudatus fuse. Here the large cells are found among and on both sides of the optic radiations, coming thus into contact with the bed of the stria terminalis and the tail of the caudate. Large globus pallidus cells are found as far ventrally in the sections as internal capsule bundles and nearly as far as the putamen is recognized. They thus come into close relation with the medial and central nuclei of the amygdaloid complex, but should not be confused with them.

In the opossum the globus pallidus holds relations very similar to those in the rabbit. Following a series of transverse sections from behind forward we find beneath the caudal border of the internal capsule (fig. 55) immediately lateral to the stria terminalis bundles and between them and the fused putamen-caudate, a small collection of large cells. These are in immediate contact with the large central nucleus of the amygdaloid complex. Immediately forward this small mass expands into a typical globus pallidus pierced by the lower bundles of the internal capsule and bounded externally by the putamen and dorsally by the compact internal capsule. The cells are large and deeply stained, but because the cells are fewer in number the whole body appears lighter than the putamen. Especially large cells are grouped in an irregular plate next to the putamen (fig. 56). Beneath the internal capsule the globus pallidus seems to extend mesad toward the supraoptic region. This apparent connection with the brain stem does not seem to extend back to the hypothalamus as in the rabbit. Continuing forward the globus pallidus is not as large as in the rabbit. Its relations are well shown in figure 57. When the anterior commissure appears the globus pallidus is wedged in the angle between this and the internal capsule, medial to the lower border of the putamen (fig. 58). It is scarcely to be recognized as a special body farther forward than this.

The globus pallidus of the turtle was seen some years ago and referred to in the following words ('15 b, p. 405): "Among the fascicles of the internal capsule which come from the sensory bundle of the crus are found many cells conspicuously larger than the ordinary cells of the lentiform nucleus. They may prove of importance in further comparisons with the mammalian brain." In figure 80 is given a photograph of a part of the lentiform nucleus. From this it is evident that these large cells are situated deep in the internal capsule below the level at which it breaks up into small bundles to traverse what we now call the putamen. This group of cells corresponds so closely to the globus pallidus as described in the rabbit and opossum that there can scarcely be any doubt about the homology.

In selachians also a collection of large cells is found which can be regarded as the forerunner of the globus pallidus. In the last section on the putamen the conclusion was reached that the 'somatic area' in the lateral wall of the telencephalon medium in selachians is homologous with the lentiform nucleus or part of it. In the description of the selachian brain ('11 a) attention was called to the presence of a considerable number of unusually large cells in the 'somatic area.' These cells are located in the course of the fiber bundles which connect the 'somatic area' with the thalamus. If this caudal part of the somatic area lying in the telencephalon medium is properly regarded as the homologue of the lentiform nucleus, then there is strong ground for considering these large cells as the equivalent of the globus pallidus.

The development of the corpus striatum from selachians to mammals may be summarized as follows: The ventro-lateral wall of the forebrain in selachians contains, 1) a lateral olfactory nucleus related to the lateral olfactory tract; 2) a deep gray mass lateral to the ventricle of the tuberculum olfactorium which may be regarded as the ventricular aspect or counterpart of the lateral olfactory area; and, 3) a large area in the telencephalon medium which is connected by ascending and descending fibers with the thalamus. The first of these gives rise to the pyriform lobe and other structures which do not enter into the corpus striatum. The second is an olfactory center which in selachians has been vaguely assigned by various authors to the 'striatum.' It retains its olfactory function and in reptiles and mammals comes to lie above the growing internal capsule, extending from the nucleus olfactorius anterior and parolfactory area to the temporal lobe. In front it includes the larger part of the 'head of the caudate' and is continuous with the nucleus accumbens (Ziehen, Kappers). Behind it expands into the central and medial nuclei of the amygdaloid complex. This elongated olfactory center forms the bed for longitudinal fibers which first clearly appear in reptiles. These are the stria terminalis. The bed of the stria comes to be attenuated throughout its course over the internal capsule, but its anterior and posterior ends remain large and important olfactory nuclei.

The somatic nucleus of the selachian retains in higher forms its relation to the thalamo-cortical tracts, forming the bed of the internal capsule in the turtle, opossum, and mammals. Its larger lateral portion, consisting usually of small cells without regular arrangement, becomes the putamen. Its deep group of very large cells is conspicuous in reptiles, marsupials and mammals as the globus pallidus.

One chief element of the corpus striatum, the nucleus caudatus, is not recognizable in the selachians. Until more complete studies of the Dipnoi are available we must regard the caudate as a structure which makes its appearance as a distinct nucleus first in reptiles. It is already so well formed in the most primitive of living reptiles that it seems very probable that it is present in the Dipnoi. In a photograph published by Elliot Smith ('08, fig. 2) there appears a slight thickening of the lateral wall of the hemisphere of Lepidosiren which projects into the ventricle and may be comparable with the dorsal ventricular ridge of the turtle. The caudate in the turtle arises as an infolding of the lateral border of the general pallium. It has the same origin in early human embryos. The caudate is connected with lower centers by both ascending and descending fibers running in the internal capsule. It is therefore to be regarded as an offshoot of or a part of the general pallium, perhaps with functions of a somewhat lower order. This relationship Elliot Smith has expressed by use of the term 'hypopallium.' The caudate and putamen enter into close relations and have a similar structure in mammals, but the two must be regarded as independent nuclei. The grounds for this are that the putamen and globus pallidus are much older phylogenetically than the nucleus caudatus and that the caudate and lentiform nuclei have a separate origin in ontogenetic development.

Functionally the corpus striatum is not a unit. The oldest structures in it, the bed of the stria terminalis and the nucleus lentiformis, are respectively olfactory and somatic sensory or correlating. To the somatic nucleus there is added later in phylogeny a secondary derivative from the general or somatic pallium, the nucleus caudatus which becomes closely related to the nucleus lentiformis both functionally and morphologically. For a clear understanding of the corpus striatum the important points to be emphasized are the derivation of the bed of the stria terminalis from the primitive olfactory centers and its present close relation to those centers, and the late derivation of the nucleus caudatus from the border of the general pallium.

If the terms palaeostriatum and neostriatum are used, it should be understood that the palaeostriatum includes putamen, globus pallidus and the bed of the stria terminalis, while the neostriatum includes only so much of the nucleus caudatus as is derived from the pallium and excludes that part of the 'head of the caudate' which is related to the stria terminalis, nucleus accumbens and the bed of the anterior commissure.

2. THE TUBERCULUM OLFACTORIUM, DIAGONAL BAND, AND ANTERIOR PERFORATE SPACE

In selachians the medial olfactory area is very much larger than the lateral, extending from the peduncle around the lower half of the rostral wall and in the medial wall back to the anterior commissure. The great reduction of this area in higher forms is correlated with the movement of the olfactory bulb and peduncle from a lateral to the rostral position. There is a large saucer-shaped basal area whose borders meet the medial and lateral olfactory areas medially, rostrally and laterally, while caudally it ends at the level of the anterior commissure. I have named this basal area ('11 a, p. 9) because of evidence that it represents more than the tuberculum olfactorium of mammals.

In reptiles and mammals the medial olfactory area becomes very much reduced while the lateral area becomes relatively more important and gives rise to the pyriform lobe, a great center for correlation with the general pallium. From the medial olfactory area of the selachian brain have been derived the medial parolfactory nucleus and possibly the anterior olfactory nucleus. The anterior olfactory nucleus is a body lying at the base of the olfactory peduncle which varies greatly in size. In the turtle ('15 b) there is at the base of the peduncle a single massive nucleus forming the floor of the ventricle and covered basally by the tuberculum. The depression of the floor of the ventricle into a deep groove in the tuberculum divides this single nucleus into the parolfactory area and the lateral body which forms part of the head of the caudate and which is described in this paper as the bed of the stria terminalis. A deep massive nucleus having the same relations is found in the opossum. In the medial wall in contact with this nucleus and between the tuberculum and the primordium hippocampi is the medial parolfactory nucleus (figs. 60, 61). Probably both of these have been derived from the medial olfactory area of the selachian. The deep mass is the anterior olfactory nucleus which represents the more lateral portion of the medial area in the selachian, where medial and lateral areas meet at the base of the peduncle. The medial parolfactory nucleus corresponds to the remainder of the medial area, greatly reduced. In the opossum the medial parolfactory nucleus seems to be continuous with the nucleus of the diagonal band.

In the rabbit the mass corresponding to the anterior olfactory nucleus seems in Weigert sections to be a forward continuation of the head of the caudate, in the lateral part of which runs the olfactory bundle of the anterior commissure. In sections stained with a Nissl stain, however, a sharp line of distinction is seen where the lamina of medial olfactory tract fibers leaves the anterior commissure bundle to go into the parolfactory area (and through it to the hippocampus) (figs. 64, 65). The cells in front of this including those surrounding the olfactory commissure bundle are large, have large nuclei and very dense chromatin content so that they stain as deeply as those of the pyriform cortex. Such cells appear on the basal surface in front of the tuberculum olfactorium and this area is traversed by bundles of the lateral olfactory tract. This basal area anterior to the tuberculum belongs to the lateral olfactory area. The large cells which appear beneath the olfactory commissure and along the lower edge of the external capsule are deep cells of the tuberculum olfactorium. On the medial surface in front of the area traversed by the medial olfactory tract above mentioned is an area of medium sized cells taking a moderately deep stain which belong to the medial parolfactory nucleus. The only body which can be called anterior olfactory nucleus in the rabbit is the mass in front of the depression of the ventricle in the tuberculum olfactorium which is common to the head of the caudate nucleus and the lateral parolfactory nucleus (figs. 63, 64, 65). The same is true of other mammals and man.

The basal area in selachians is much more extensive than the tuberculum olfactorium of higher forms. The aberrant vertebrate classes, ganoids, teleosts and amphibians have no highly specialized tuberculum olfactorium. The dipnoans stand in the line of descent between selachians and reptiles. Elliot Smith ('08) has called attention to the relatively enormous tuberculum olfactorium in Lepidosiren. In early stages of development this forms a great sac bulging ventro-rostrally which strongly reminds the writer of the basal area of the selachian. The forebrain of reptiles and mammals is characterized by the great expansion of the general pallium and the further development of the lateral olfactory area. From the rostral part of the basal area of selachians is formed the tuberculum olfactorium of reptiles and mammals. From its caudal part, I believe, arise the gray of the anterior perforate space and the diagonal band. My reasons for this conclusion are as follows:

The basal area in selachians is intermediate between the medial and lateral olfactory areas, its borders being intimately fused with those areas. The lateral area elongates with the hemisphere in reptiles and mammals and gives rise to the pyriform lobe and part of the amygdala in the temporal pole. At the same time a connection is maintained between the amygdala and the medial olfactory area in front of the anterior commissure. This connecting band is the diagonal band of Broca. In selachians all connection between medial and lateral areas which could be compared with the diagonal band is included in the basal area. It is also noteworthy that a broad diffuse fiber tract called by the writer ('11 a) the tractus olfactocorticalis septi connects the whole medial border of the basal area with the hippocampal pallium. A similar tract arises from the tuberculum olfactorium in mammals. Fibers arising from the caudal part of the basal area and from the lateral area and following this course are comparable with the fiber tract of the diagonal band in reptiles and other mammals.

The anterior perforate space is an ill-defined region on the base of the human hemisphere which has been much discussed. As an area through which arteries penetrate the brain, it is easily recognized but its neurological relations and significance are more obscure. It lies at about the level of the anterior commissure and is bounded medially by the fissura prima and diagonal band, laterally by the sulcus endorhinalis and rostrally by the tuberculum olfactorium. When this area is examined microscopically it is difficult to establish differences between it and the tuberculum olfactorium. Cajal ('04, p. 993) identifies the anterior perforate space of man with the tuberculum olfactorium of other animals.

In human foetal brains there is clearly a band of tissue continuing from the tuberculum olfactorium into the temporal pole, lying medial to the sulcus endorhinalis. In describing the relations of the amygdaloid complex below, I shall show that this band is present also in the turtle, opossum and bat, and that it includes the area corresponding to the anterior perforate space. In the turtle this band passes forward independently of the tuberculum olfactorium, while in mammals it joins the lateral border of the tuberculum. In the rabbit and other adult mammals this band is interrupted at the level of the optic chiasma. In these brains the anterior perforate space is continuous and identical in structure with the cortex of the tuberculum. The gray of the anterior perforate space must be a derivative either of the primitive lateral olfactory area or the basal area of selachians.

If we examine the anterior two-thirds of the lateral olfactory area in reptiles and mammals we find it divided lengthwise by the sulcus endorhinalis.

Now in selachians the lateral olfactory area has large cells and is traversed by the lateral olfactory tract, while the basal area is small celled and is penetrated by diffuse end fibers of that tract. There is no definite sulcus endorhinalis in selachians. The suggestion made here is that the sulcus endorhinalis has been formed along the line of junction of the basal and lateral olfactory areas and that the narrow small-celled area medial to the sulcus in reptiles and mammals represents the lateral portion of the basal area of the selachian.

This hypothesis would explain the continuity of the cortex of the perforate space with that of the tuberculum olfactorium (figs. 66, 67) and the presence in the human foetal brain of foldings and island formations in the perforate space as in the tuberculum olfactorium. It also gives a definite status to the narrow band of so-called lateral olfactory area medial to the sulcus endorhinalis and affords an explanation for the appearance of this sulcus within the supposed lateral olfactory area. Finally, it is consistent with the differences in structure between the parts of the pyriform lobe medial and lateral to the sulcus.

In the elongation of the olfactory areas brought about by the expansion of the hemisphere under the influence of the growing general pallium, the basal area of the selachian brain is stretched back into the temporal pole parallel with the lateral olfactory area. The basal area gives rise not only to the tuberculum olfactorium whose characteristics it already shows in a primitive degree, but also to the anterior perforate space, the diagonal band and that part of the so-called lateral olfactory area which lies medial to the sulcus endorhinalis.

The large basal area in selachians which shows some island formation is involved in the evolution of a great complex of nerve centers the full significance of which can not be understood until the morphology and functional relations of the amygdaloid complex of mammals are taken into account. The basal area has a strong fiber connection with the pallium in selachians but whether this involves the general pallium can be made clear only by an extension of Holmgren's work on the selachian pallium. It is clear from the present study, however, that the bodies derived from the basal area and the adjacent lateral olfactory area, do in mammals provide for extensive correlation with the general pallium. The residuary part of the basal area which in reptiles and mammals we call the tuberculum olfactorium is strongly related by fiber tracts with these somatic correlating centers (see discussion of amygdaloid complex later). Island formation is not confined to the tuberculum olfactorium, but may be seen in human embryos in the anterior perforate space and the cortical amygdaloid area; also in Didelphys in one of the special amygdaloid nuclei. It seems probable, then, that while the equivalent of the tuberculum olfactorium appears more closely related to the medial olfactory area in selachians, it comes to be dominated in the dipnoan-reptilian-mammalian line by the growing influence of the somatic correlations through the lateral olfactory area (pyriform lobe) and has its chief significance in mammals as a part of the olfacto-somatic correlating mechanism. In the ganoid-teleost and the amphibian lines this somatic correlation is not so highly developed and the tuberculum olfactorium has not passed beyond the primitive condition seen in selachians.

The diagonal band

The relations of the diagonal band are important for an understanding of the amygdaloid complex.

Turtle. The diagonal band of the turtle has been described in a previous paper ('15 b). At the medio-basal angle the fissura prima separates the diagonal band from the tuberculum. Horizontal sections recently prepared confirm the previous description of the continuation of the nucleus on the basal surface to join the amygdala. In its relations and the degree of its distinctness from other structures this nucleus in the turtle agrees better with that of the rabbit than that of the opossum. On the basal surface, however, it is much less rich in cells than it is in mammals.

Opossum. The nucleus of the diagonal band is not sharply distinguished from the medial parolfactory nucleus. In transverse sections some distance in front of the anterior commissure the medial parolfactory nucleus lies in the medial wall below the fimbrio-dentate sulcus (Johnston, '13 b, p. 387, fig. 28) and meets the tuberculum olfactorium below. At this point is presented the very striking condition that a thick band of tuberculum cells extends up from the medial edge of the tuberculum between the medial and lateral parolfactory nuclei (fig. 60). This band of cells converts the appearance of the tuberculum in transverse section, from that of a saucer to that of a deep bowl. The cells of the medial parolfactory nucleus are in irregular rows conforming to the vertical fibers of the precommissural system in which they are imbedded. Following this body caudad in the sections, it bends round a short distance on to the basal surface and in a section just in front of the anterior commissure (fig. 59) the upper end of the nucleus is seen just below the fimbrio-dentate sulcus among the precommissural fibers which are entering the alveus, while the isolated lower end of the same nucleus appears at the medio-ventral angle of the hemisphere in contact with the tuberculum olfactorium. In this section the nucleus must be considered as the equivalent of the nucleus of the diagonal band as described in the rabbit and man below. In the opossum it is intimately related to the medial parolfactory nucleus. The fissura prima is only slightly developed in the opossum. It separates the diagonal band from the tuberculum olfactorium at the medio-basal angle, but no distinct line of separation can be found between the diagonal band and the medial parolfactory nucleus. In this respect the opossum preserves primitive conditions even to a greater extent than the turtle, for the diagonal band must be regarded as a part of the primitive olfactory nuclei which connected the medial and lateral olfactory areas around the basal surface of the forebrain. The lateral area having been carried back into the temporal pole, the diagonal band continues to connect the medial (anteriorly placed) olfactory area with the temporal part of the lateral area. In the turtle and mammals that portion of the nucleus which accompanies the precommissural fiber system in the medial wall becomes separated from the parolfactory nucleus; in the opossum it is not.

The nucleus of the diagonal band turns on to the basal surface medial to the tuberculum olfactorium, and at the caudal border of the tuberculum spreads laterally as far as the sulcus endorhinalis. Here it fills the broad space beneath the internal capsule and anterior commissure (fig. 58). Its boundaries are poorly defined. It should be noted that in this region that part of the lateral olfactory area lying medial to the sulcus endorhinalis continues from the lateral border of the tuberculum olfactorium back to the nucleus of the lateral olfactory tract. At the level of this nucleus (fig. 58) the lateral olfactory area enters into the infolding which forms especially the lateral amygdaloid nucleus. From this level caudad the nucleus of the diagonal band can not be distinguished from the amygdaloid nuclei.

Rabbit. It was in studying the rabbit brain several years ago that the importance of the cells accompanying the fibers of the diagonal band became evident. This was referred to in the paper 1915 b as follows: "It may be spoken of as the nucleus of the diagonal band. In mammals this consists of a thin plate of closely packed cells which extends from a point rostral to the anterior commissure down in front of the optic chiasma and caudad on the latero-basal surface to the amygdaloid complex." A more detailed description follows:

In a horizontal section which cuts the hippocampal commissure near its lower border a small collection of very darkly stained cells is seen in close relation to the precommissural fornix (fig. 62). The cells on each side form a continuous column from this point to its fusion with the amygdaloid complex. Lower in the medial wall the paired nuclei are flattened against one another in the median plane. The cells of this nucleus are not small as in the turtle, but distinctly larger and more deeply stained than those of the parolfactory nuclei. They lie intermingled with a mass of fibers part of which come from the medial olfactory tract and nuclei (fasciculus marginalis) and part from the medial forebrain bundle and the diagonal band. The whole system of fibers is the precommissural system of Elliot Smith.

In sections through the anterior commissure (figs. 64, 65) the nucleus thickens at its caudal border while its anterior border remains thin and lies in the course of the fasciculus marginalis. One would think from these sections that this tract passes through the parolfactory nuclei to be related chiefly to this nucleus. Opposite the lower border of the anterior commissure (fig. 66) the two nuclei form a large triangular area and each nucleus comes to the surface in the median sagittal fissure. From this point basalward the column of cells and fibers may be seen on the surface of the entire brain and corresponds to the gyrus subcallosus of the human brain. It should be noticed that between these nuclei and the anterior commissure there is a mass of small cells belonging to the commissure bed and continuous at either side with the bed of the stria terminalis and nucleus accumbens.

In a section close to the base of the frontal pole (fig. 67) passing through the tuberculum olfactorium, the nucleus of the diagonal band is more rounded and is very distinct in structure from either the tuberculum or the paraterminal body. Its cells are mostly large, are closely packed and deeply stained, while those of the surrounding nuclei are smaller and paler. The fissura prima bounding the diagonal band in front is now clearly marked.

In a section through the preoptic recess the diagonal band lies fully exposed in the sagittal fissure. Its fibers appear to enter into the medial forebrain bundle which here passes backward as a broad band from the tuberculum olfactorium and the parolfactory area. The cortex of the tuberculum seems to extend from the fissura prima around to the sulcus endorhinalis where it meets the pyriform cortex. The lateral part of this is primitive olfactory area, not differentiated as tuberculum, and belongs to the anterior perforate space. Large cells which lie close to the tuberculum cortex are here seen scattered among the fibers of the medial forebrain tract because this section passes so near the surface of the tuberculum.

From this level the diagonal band bends latero-caudad and rapidly extends toward the temporal limb of the anterior commissure. The diagonal band partly crosses ventrally of the medial forebrain tract, partly is interwoven with it. The cells form an elongated area and some isolated clumps are seen near the anterior commissure. The only cells with which these could be compared are the large cells of the globus pallidus, but these recede as the diagonal band advances in this region so that there is no doubt as to the limits of either. As the olfactory tubercle disappears from the sections the diagonal band grows broader and fills most of the area between the preoptic recess and the sulcus endorhinalis. The surface, however, from the fissura prima to the sulcus endorhinalis is still covered by the cortex of the anterior perforate space which is indistinguishable in appearance from that of the tuberculum. The diagonal band cells and fibers now fill nearly the whole area medial to the sulcus endorhinalis and the anterior commissure bundles. A few sections farther on the cortex of the perforate space suddenly disappears (fig. 68). Now the diagonal band fills the whole space from the preoptic region to the sulcus endorhinalis and the fissura prima has disappeared. The lateral olfactory area medial to the sulcus endorhinalis is absent from the level of the preoptic recess to the nucleus of the lateral olfactory tract which represents this area in the temporal pole. This will be described in connection with the amygdaloid complex.

At the level which we have now reached in these sections the central and medial nuclei of the amygdaloid complex are formed (fig. 68). The description of this region will be completed under the head of the amygdaloid complex. The diagonal band is a clearly separate entity to this point, but from here on basalward in the temporal pole it merges insensibly with the central and medial amygdaloid nuclei.

The general disposition of the diagonal band in the bat is the same as in the rabbit. The cells in the medial hemisphere wall as seen in a parasagittal section are figured in '13 b, fig. 46. In transverse sections the diagonal band nucleus is shown in figures 78, 79. In these sections nearly the whole course of the nucleus is shown from near the neuroporic recess to the amygdaloid complex. It is interesting to notice how the latero-caudal end of the nucleus bends up beneath the lateral limb of the anterior commissure. A few sections farther back, the diagonal band cells crowd up beneath the anterior commissure very much as they do in the human foetal brain. The relation of this to the infolding along the line of the sulcus endorhinalis will be described in connection with the amygdaloid complex and it will there be shown that in the bat the lateral olfactory area medial to the sulcus endorhinalis is continuous from the temporal to the frontal pole, but that here for a few sections it is involved in this infolding and does not appear on the surface.

Human foetal brains. The gray matter in the foetus of 175 mm. is not far enough differentiated for the study of the nucleus of the diagonal band. This foetus does show, however, in transverse sections, complete continuity of the lateral olfactory area from the tuberculum to the nucleus of the lateral olfactory tract. The same condition is found in several other foetal brains which I have studied. The lateral olfactory area runs along the lateral border of the diagonal band and constitutes the anterior perforate space and connects this with the amygdaloid region of the temporal pole. Here it is represented by the nucleus of the lateral olfactory tract and enters into the formation of the amygdaloid complex. This condition in the foetal human brain agrees more nearly with that in the bat and the opossum than with other adult mammals.

The foetus of the eighth month shows the structure and relations of the nucleus of the diagonal band with remarkable clearness. That part of it which lies in the gyrus subcallosus corresponds so closely to that in the rabbit that extended description is unnecessary. Five sections are shown in figures 93 to 97. Beginning at the lower border of the septum pellucidum near the locus of the neuroporic recess the nucleus of the diagonal band descends in the gyrus subcallosus and turns backward in the basal surface in the direction of the temporal pole. Here it is bounded laterally by cortex which appears the same as that of the tuberculum olfactorium. This is the anterior perforate space.

In a section near the brain base (fig. 94) the cells of the diagonal band extend laterally close beneath the internal capsule to the temporal limb of the anterior commissure. The cells are larger than those of any of the groups in the section and are so deeply stained as to be very conspicuous. They are arranged somewhat in rows between the fiber bundles of the band. In front of this nucleus are the dense masses of granules—islands of Calleja—belonging to the deep layers of the tuberculum olfactorium. Among the fibers are seen some small dense bundles part of which turn into the tuberculum olfactorium. These come from the amygdaloid complex and will be described later (p. 448). Within ten sections from the last, the nucleus of the diagonal band has become a fairly dense mass whose lateral border reaches even behind the temporal limb of the anterior commissure and comes in contact with the external capsule (fig. 95). All the sections between the last two figures show much the same arrangement as this one and all show bundles passing obliquely through the diagonal band on their way between the tuberculum olfactorium and the amygdala. Another interesting bundle shows in both these figures. In figure 94 (x) just below and medial from a prominent artery is a group of small bundles which appear to join the medial forebrain bundle on its way to the hypothalamus. In figure 95 (x) these same fasciculi are seen to the right of the artery and imbedded among diagonal band cells. This is a tract of considerable importance, many additional fascicles of which appear in adjacent sections (figs. 96, 97, x). Most (perhaps all) of the fascicles join into larger bundles which take a position on the rostral side of the anterior commissure just where it joins the external capsule. Here these bundles descend with the anterior commissure into the temporal pole.

These fibers require further study. They may represent a part of the primitive tractus olfacto-hypothalamicus arising in man from the pyriform cortex, following the temporal limb of the anterior commissure and bending down in the medial forebrain bundle to the hypothalamus. Other bundles related to the anterior commissure will be mentioned in the section on the amygdala (system y, p. 449).

In sections following this the bundles just described (x) are imbedded in a dense mass of diagonal band cells medial to the anterior commissure (fig. 96), and this is continuous with another dense collection at the caudal border of the commissure bundle. This last group comes into direct contact with the putamen whose cells appear only as small granules in comparison with the diagonal band cells. Figure 97, which shows the lowest part of the gyrus subcallosus lateral to the preoptic recess, shows also the extreme extent of the diagonal band nucleus on the medial surface of the anterior commissure and in contact with the putamen. A partly isolated group of cells lies medial to this directly over the central nucleus of the amygdala which will appear here in the following sections. Some fifteen sections below the last (fig. 98) the nucleus of the diagonal band has disappeared except for two small groups of cells between the anterior commissure and the central and medial nuclei of the amygdala which continue about ten sections farther. The superficial fiber layer of the diagonal band continues for some sections in the general direction of the anterior commissure and finally disappears. It seems in this brain to be related chiefly or wholly to the central amygdaloid nucleus.

The basal proliferation of cells seen in early human embryos (18, 26 and 33 mm., figs. 1, 2, 3, 10) referred to on page 379 may now be regarded as a common anlage for the tuberculum olfactorium anterior perforate space and perhaps the nucleus of the diagonal band, these structures forming at first a continuous body extending from the base of the olfactory peduncle to the amygdaloid area in the temporal pole.

In brief summary, the diagonal band consists of a nucleus of gray matter probably derived from the basal area of the selachian brain and intimately related to the medial olfactory area, and of a tract of mostly diffuse fibers. Most of these fibers join the precommissural system and connect the amygdaloid complex with the hippocampal formation. With these are mingled fibers which connect the amygdala and tuberculum olfactorium. Other fibers which mingle with the anterior commissure as they are distributed to the temporal cortex pass through the diagonal band. The diagonal band thus represents the caudal border of the whole system of olfactory centers in the hemisphere (the preoptic nucleus being in the telencephalon medium) and maintains the primitive connection between the lateral olfactory area and the hippocampal formation. The preservation of this connection through all the form changes of the hemisphere is due to the growing importance of the lateral olfactory area and especially its new significance in relation to the general pallium which will be discussed in connection with the amygdala.

3. COMPOSITION OF THE STRIA TERMINALIS

An examination of the connections established by the several bundles of fibers which make up the stria terminalis is desirable before undertaking the analysis of the amygdaloid complex. I shall begin with the opossum as a form which is favorable for study and at the same time presents in fairly complete form the elements typical of the stria in mammals.

Just above and behind the anterior commissure, where the stria bed is large and the bundles are not closely packed, the disposition of the individual bundles can be clearly seen in both transverse and sagittal sections stained by the Weigert method. The following bundles are recognized (fig. 20):

1. The commissural bundle. This comes forward in the deepest part of the stria next to the internal capsule and presents a rather wide curve laterally as it turns into the commissure, where it forms a thin layer on the caudo-ventral surface (fig. 22). This is a commissure of the nucleus of the lateral olfactory tract.

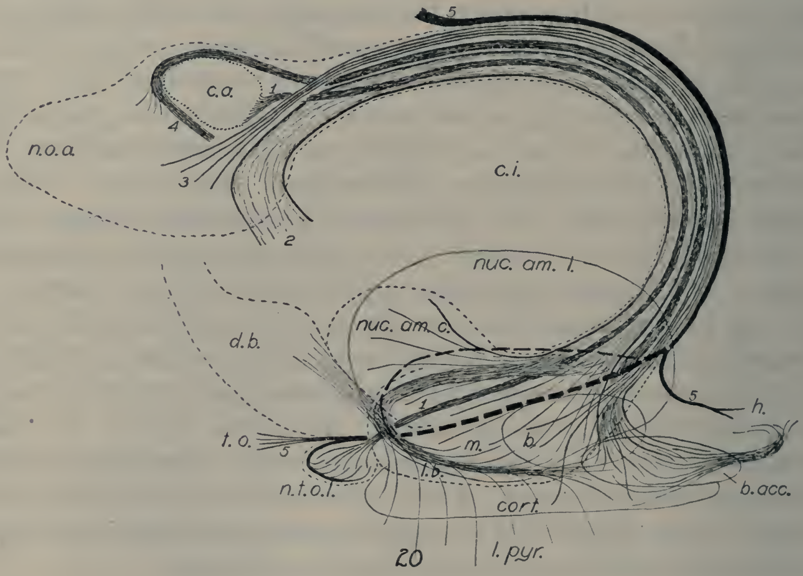


Fig. 20 A diagram to show the component bundles of the stria terminalis in the opossum. The diagram represents the stria of the left side as seen from the lateral aspect. The bed of the stria together with the central and medial amygdaloid nuclei, the nucleus of the lateral olfactory tract, the diagonal band and the anterior olfactory nucleus are outlined in broken lines; the lateral, basal, accessory basal and cortical amygdaloid nuclei are outlined in light continuous lines. The hippocampus and lobus pyriformis are indicated only by the abbreviations without outlines. The course of each bundle is described in the text (p. 382). The fibers drawn in the diagonal band are only a few of the deep fibers coming out of the longitudinal association bundle which is connected with the stria system. The stria medullaris bundle is represented as lying outside of the bed of the stria terminalis. Note its four divisions to the tuberculum, the nucleus of the lateral olfactory tract, the pyriform lobe by way of the longitudinal association bundle and the hippocampal formation.

2. The hypothalamic bundle. This is a more diffuse bundle of finer fibers among which the denser commissural bundle is imbedded. The diffuse fibers turn downward without approaching very near the anterior commissure and bend backward in the medial forebrain bundle presumably to go to the hypothalamus. This is the largest bundle and contains more fibers than any other bundle. Caudally it arises from the central and medial amygdaloid nuclei. It is the olfactory projection tract of Cajal.

3. Infra-commissural bundle. The most lateral of all the bundles at this point runs directly downward and forward beneath the anterior commissure and continues forward in the gray medial to the head of the caudate, lateral to the ventricle. Further caudally this bundle comes to be in a dorsal position just beneath the ventricle, overlying the bundle next to be mentioned.

4. Supra-commissural (parolfactory and hypothalamic) bundle. This runs forward, inclines toward the median plane, passes lateral to the fornix column, and flattens dorso-ventrally into a thin sheet over the anterior commissure. The fibers are closely applied to the commissure and most of them wrap about the commissure to its ventral surface and then join the medial forebrain bundle (fibers from parolfactory nuclei) and run on toward the hypothalamus. In front of the commissure some of these fibers go forward and downward into the anterior part of the parolfactory area. This bundle comes to lie in the deeper lateral portion of the stria beneath the infra-commissural bundles, but behind the internal capsule continues caudad and ventrad to supply the lateral part of the basal nucleus, while the infra-commissural bundle turns slightly mesad to supply the medial part of the basal nucleus.

5. Stria medullaris bundle. A short distance behind the anterior commissure the stria terminalis, stria medullaris and the fornix cross almost in contact with one another. At this point the fornix gives the large corticohabenular bundle to the stria medullaris (Johnston, '13 b, fig. 38). Here also a very compact bundle lying on the ventricular medial surface of the stria terminalis turns into the stria medullaris.

Behind the internal capsule the behavior of these bundles is as follows (figs. 21 to 31). The lateral ventricular bundle (3) bends downward and slightly medially and its fibers spread out in the basal nucleus continuing far forward in it. The deeper lateral bundle (4) bends downward and then sharply backward between the central and the accessory basal nucleus and is distributed to the accessory basal nucleus back to the point of meeting of this nucleus with the hippocampus. From this nucleus fibers gather and form a bundle running backward and then turning up into the hippocampus at the extreme caudal angle of the temporal pole (figs. 21 and 28). The medial superficial bundle (2) slips down medially on the surface of the brain

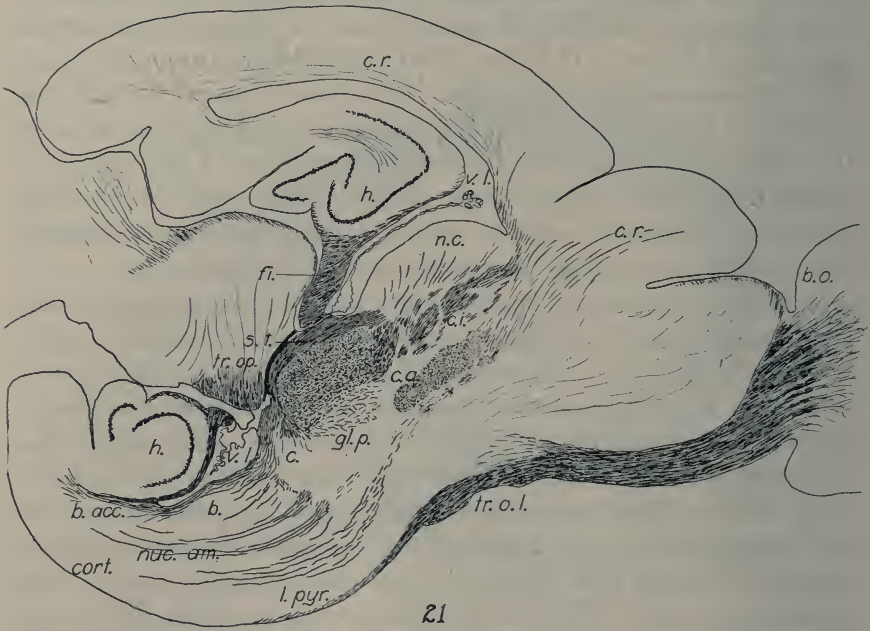
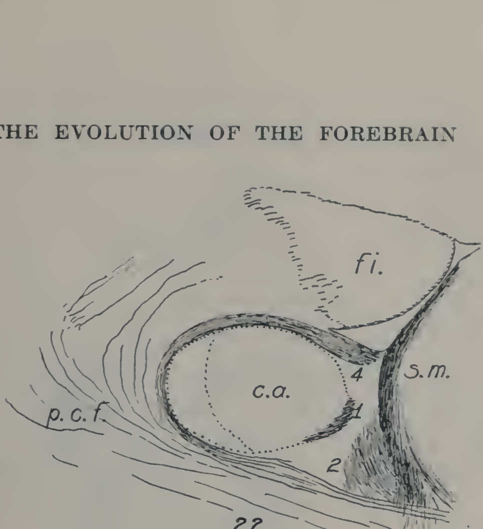
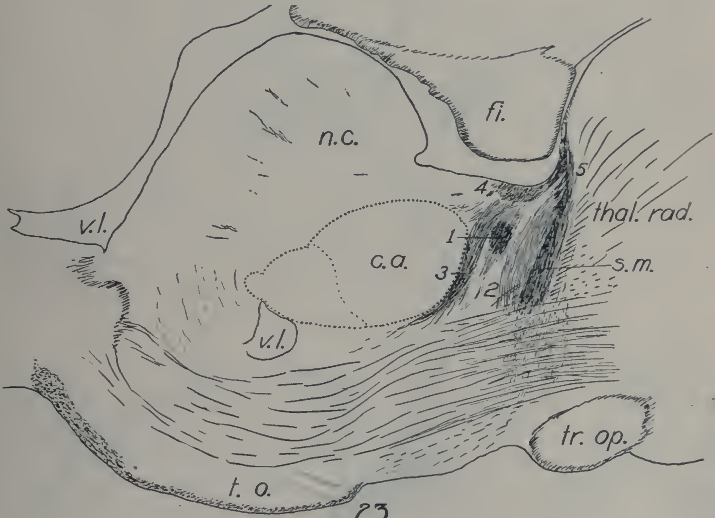


Fig. 21 A parasagittal section of the telencephalon of the opossum to show the general relations of the stria terminalis and corpus striatum. Weigert stain. In this and the following figures the nuclei of the amygdaloid complex are indicated by the last part of the abbreviation without repetition of the letters *nuc.am.* in each case. Where the stria bends around the internal capsule the stria medullaris bundle is drawn in solid black. The distribution of the several bundles to the amygdaloid nuclei is shown in more detail in the following figures. Note the outflow forward beneath the anterior commissure.



22

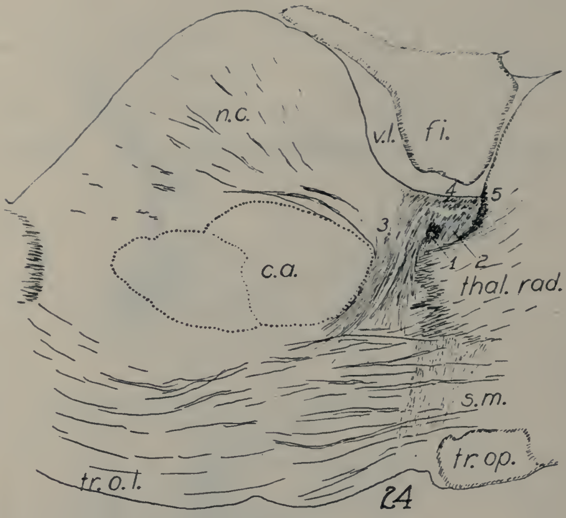


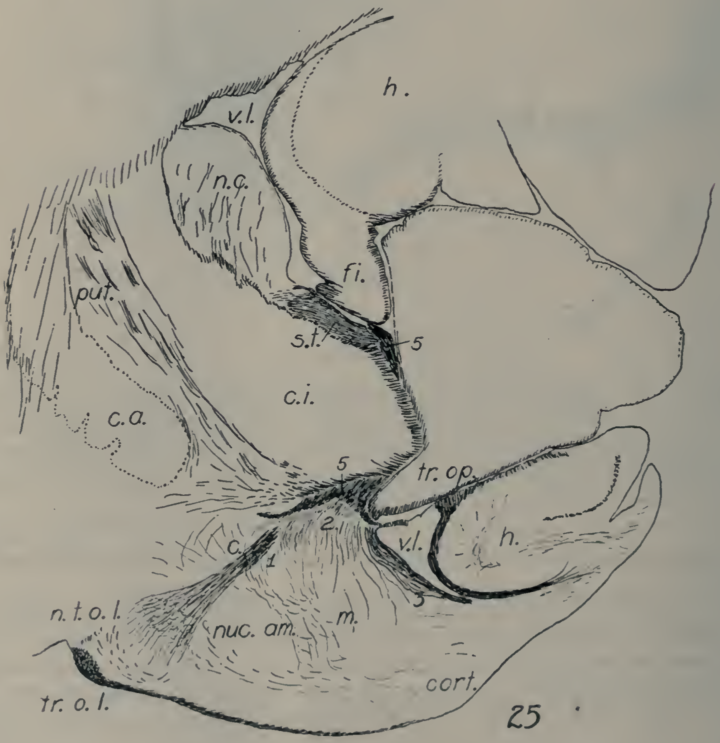
23

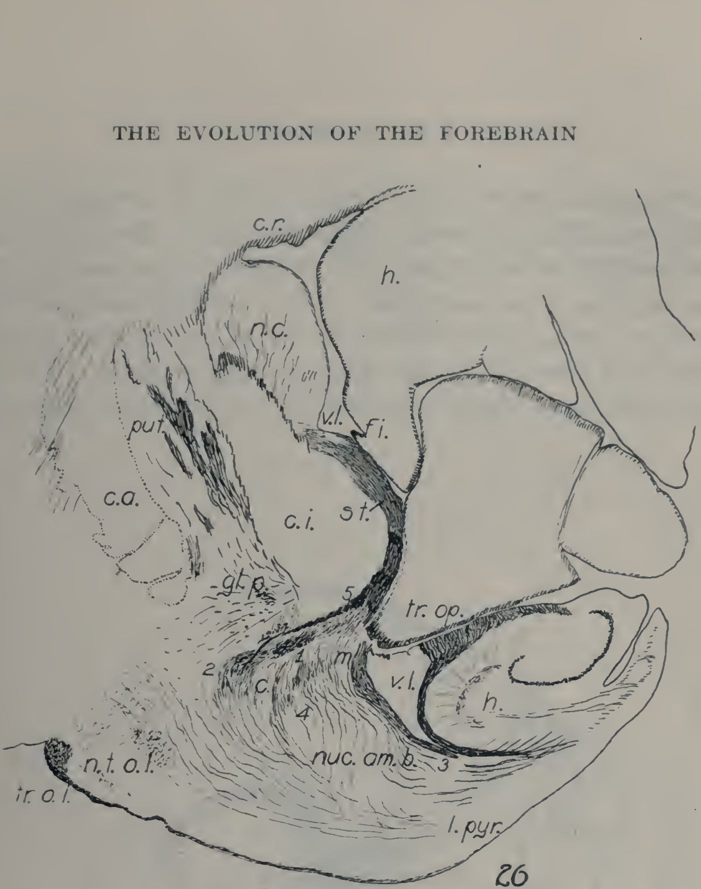
Figs. 22 to 28 Drawings from another series of sagittal sections of the opossum brain by the Weigert stain. The drawings are accurately outlined under the projection apparatus and the stria terminalis system is carefully drawn. Other structures are diagrammatically sketched. In many drawings the structures labeled *c.a.*, *c.i.*, *f.i.*, *c.r.*, and *tr.op.* would be nearly black if filled in.

Fig. 22 A section through the anterior commissure near the median plane. Two sections have been combined in order to show bundles 1 and 4 in the same drawing.

Fig. 23 A section farther laterad where all the bundles are seen in the large part of the stria bed dorso-caudal to the anterior commissure. The commissural bundle is the dense one imbedded in part of *2*. The fascicles of bundle *5* are seen coming out of the stria medullaris. Note that a large part of the stria medullaris comes up from the preoptic region, from the olfactory nuclei through the medial forebrain bundle.


n.c.
v.l.
fi.
4
5
3
1
2
c.a.
thal. rad.
s.m.
tr. op.
tr. o. l.
24


h.
v.l.
n.c.
fi.
put.
s.t.
5
c.i.
c.a.
5
tr. op.
2
c.
1
v.l.
h.
3
n. t. o. l.
nuc. am.
m.
cort.
tr. o. l.
25



26

Fig. 24 A section farther laterad showing the arrangement of the bundles as they take their place over the internal capsule (*thal.rad.*).

Fig. 25 A section through the lateral part of the internal capsule. Bundles *1* and *5* and parts of *2* and *3* appear below the capsule and all the bundles closely packed above it. The dense lamina lying on the floor of the lateral ventricle is the chief bundle figured by previous authors. It comes mostly from bundle *3* and is only a small part of the stria. The region of the central nucleus through which bundle *1* passes is very complex. In these figures only a slight indication is given of the fibers flowing out forward through this region. The peculiar form of bundle *5* is referred to in the text. The ending of its fibers in the nucleus of the lateral olfactory tract is indicated ental to the *tr.o.l.* Compare figure 20.

Fig. 26 A section slightly farther laterad showing the stria coming round the internal capsule. Note the dense fascicles of bundle *5* mingling with bundle *2* in the genu of the latter in the central nucleus. Bundle *2* extends up beneath the figure *5* so that bundle *1* is completely imbedded in it. Note that a small branch of bundle *5* appears in the thin wall of the lateral ventricle adjacent to the choroid fissure. It reaches the hippocampus between the sections drawn in figures 27 and 28. Note that fibers from the basal nucleus are running back toward the hippocampus. In the stria above the internal capsule a small blank space represents a little mass of gray.

directly opposite to the optic tract in the groove between the hemisphere and brain stem. Here the bed of the stria expands and is continuous with both the medial nucleus and the large central nucleus of the amygdala. The bundle spreads or divides into two, one going down in the medial nucleus the other spreading laterally and forward in the large central nucleus. The commissural bundle (1) lying imbedded in (2) continues close to the

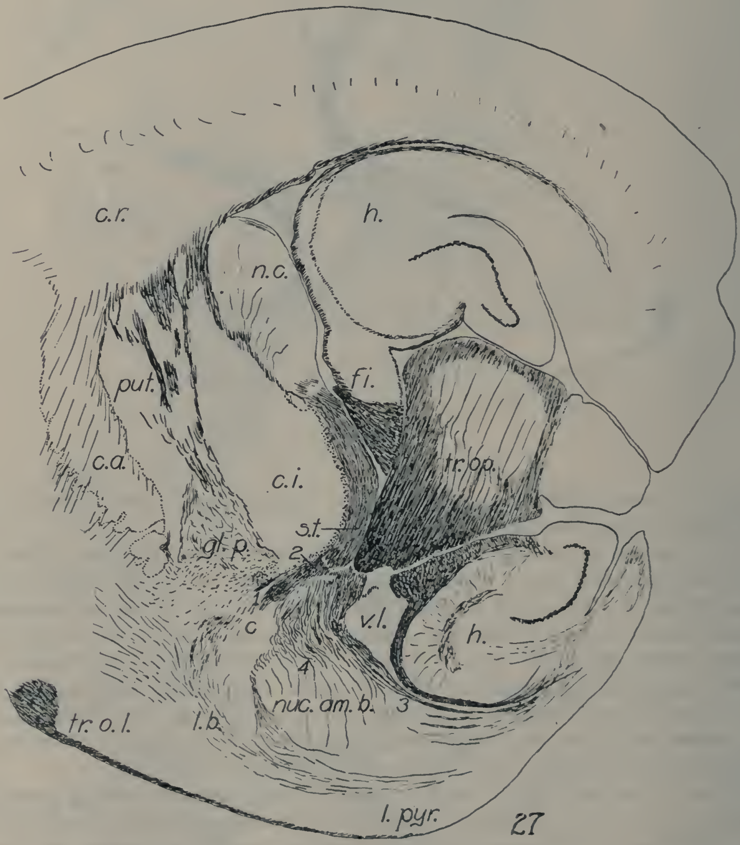


Fig. 27 A section slightly lateral to the last. In both sections the fibers of bundle *2* form a sort of genu in the central nucleus where they bend into the longitudinal association bundle. In this section some fibers of bundle *4* are seen also entering the longitudinal bundle. Comparison of this figure with figure 25 shows how distinct the commissural bundle is from this association bundle, with which it has been confused by earlier authors studying mammals. Bundle *3* in the floor of the ventricle seems to run far on toward the hippocampus.

internal capsule bending forward while bundle (2) enters its nuclei and then goes diagonally downward and forward to spread out in the compact rounded nucleus of the lateral olfactory tract (figs. 25, 33, 34).

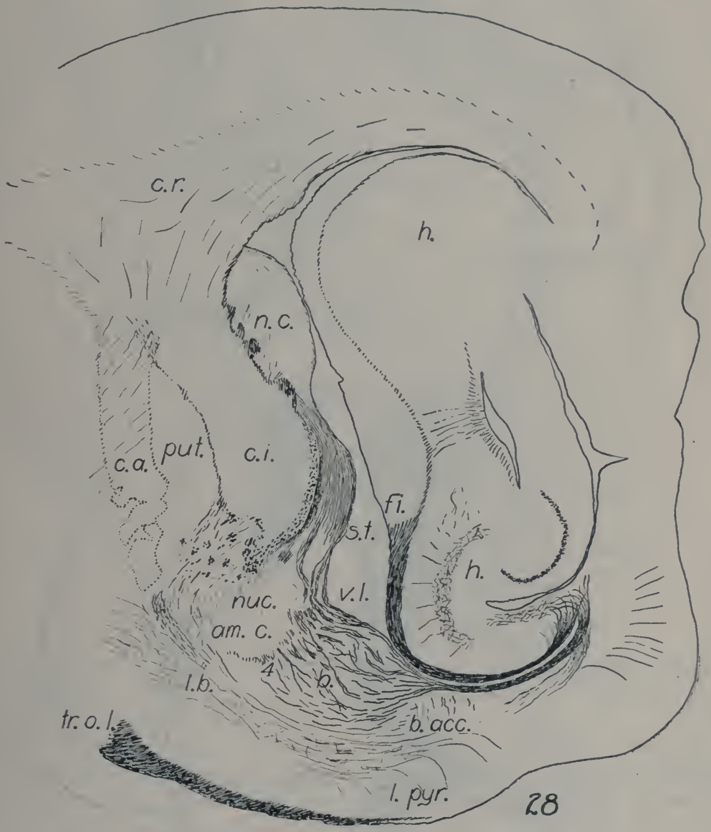
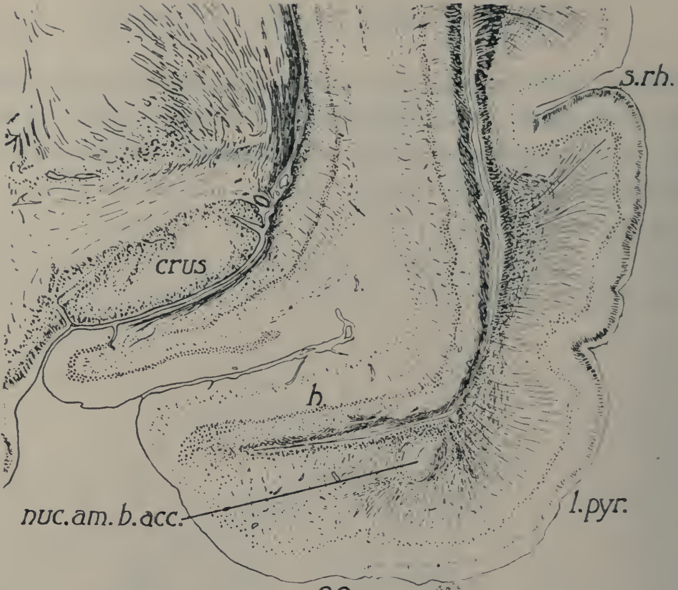
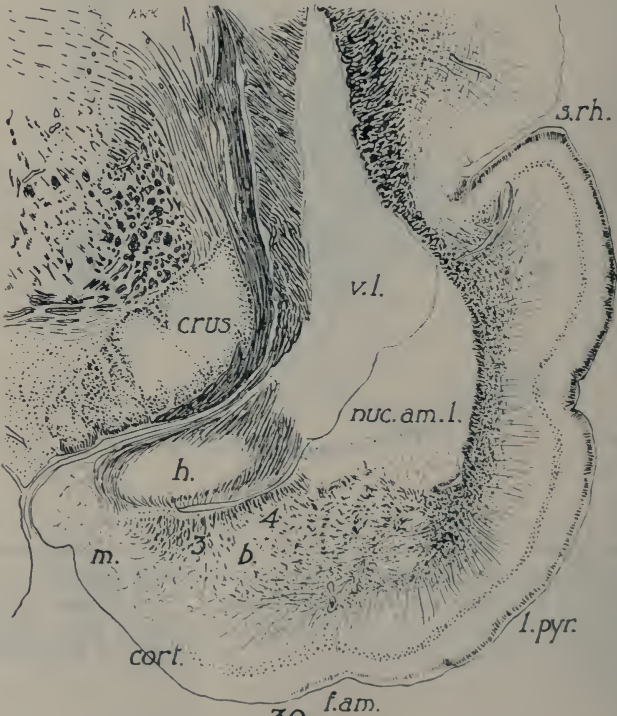


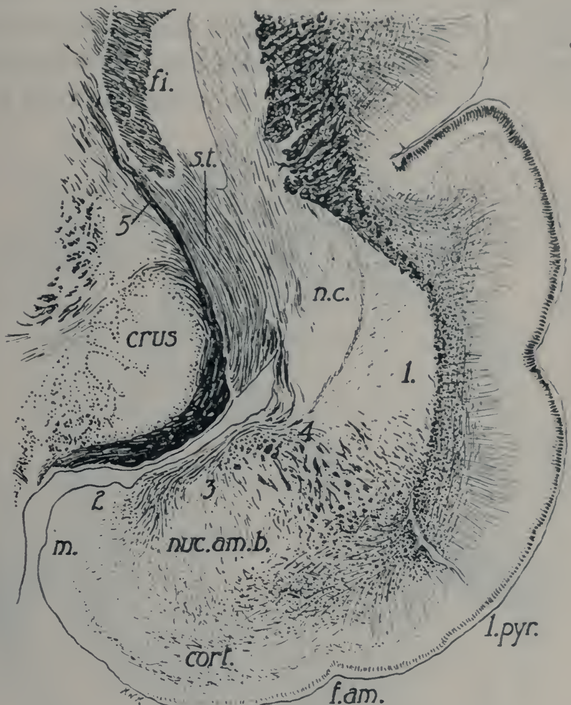
Fig. 28 A section through the extreme lateral part of the stria as it bends round the internal capsule. The section falls in the plane of the amygdalopyriform association bundle (sagittalis Längsbundel) which is only lightly sketched. This bundle is more compact as shown in the transverse sections which follow. In this section it is seen that the bundle beneath the ventricle leading to the hippocampus is probably not a direct continuation of bundle *3* or *4*, but consists of fibers arising in the basal nuclei.


s.rh.
crus
h.
nuc.am.b.acc.
l.pyr.

29


s.rh.
v.l.
crus
nuc.am.l.
h.
4
m.
3
b.
l.pyr.
cort.
f.am.

30



31

Figs. 29 to 36 Transverse sections of the brain of the opossum stained by the Weigert method. The drawings show the pyriform lobe and such adjacent structures as are discussed in this paper.

Fig. 29 Section through the level of the accessory basal nucleus amygdalæ. This appears to divide the corona radiata into an outer part related to the pyriform cortex and an inner ventricular layer related to the amygdala. Compare with figure 52.

Fig. 30 Section 1.8 mm. forward from the last. The medial, basal and lateral nuclei have appeared. The accessory basal is still present lateral to the basal. The fibers cut across between the lateral and accessory basal nuclei belong to the longitudinal association bundle. Compare with figure 53.

Fig. 31 Section 0.9 mm. forward from the last. The stria terminalis comes down over the caudal surface of the internal capsule, and bundles *3* and *4* connect with it. The stria medullaris bundle (*5*) looks as if it were a part of the optic tract. Compare with figure 54, which is a little farther forward than this.

The stria medullaris fibers follow the caudal border of the stria terminalis closely applied to the internal capsule, then descend close to the rostral border of the optic tract so that a close study of both transverse and sagittal sections is necessary to make out their course and destination. As they approach the amygdaloid complex these fibers form a flattened bundle thicker in the middle and with one thin edge spreading toward the hippocampus and the other directed forward along the lower border of the internal capsule and globus pallidus (fig. 25). Below this point the fibers in both these thin edges separate from the rest of the bundle. The caudal fibers run close along the rostral border of the choroid

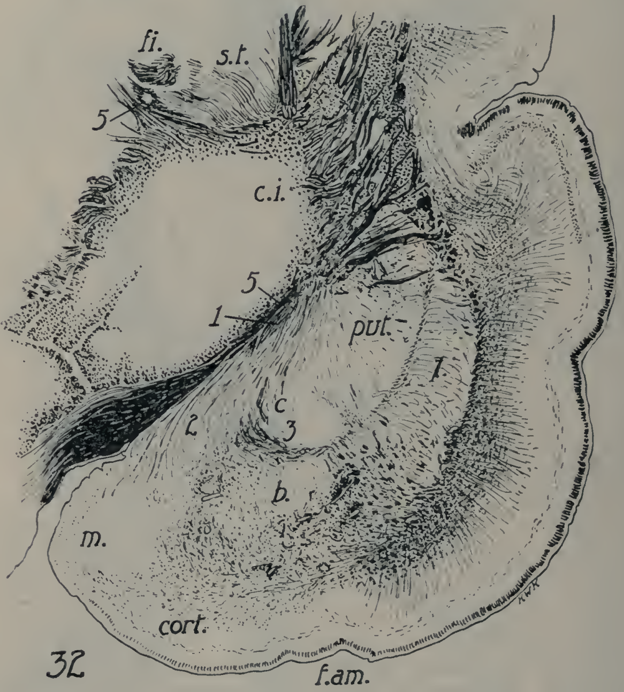


Fig. 32 Section 0.9 mm. forward from the last. The stria bed expands into the central and medial nuclei. The stria medullaris bundle (*5*) follows the border of the optic tract. The commissural bundle (*1*) is imbedded in the olfactory projection tract (*2*). Fibers of the longitudinal association system are seen cut across between the lateral and basal nuclei. Compare with figure 55.

fissure, pass beneath the end of the fissure and enter the alveus of the hippocampus. The fibers in the rostral edge of the bundle separate as several small very dense bundles and some of these at least become imbedded in the diffuse fibers of bundle 2 which turn into the longitudinal amygdalo-pyriform association bundle (fig. 26). They presumably come from the pyriform lobe to go to the habenula. The thicker middle part of the bundle now becomes closely applied to the optic tract and descends to the region of the anterior perforate space. Here they separate from

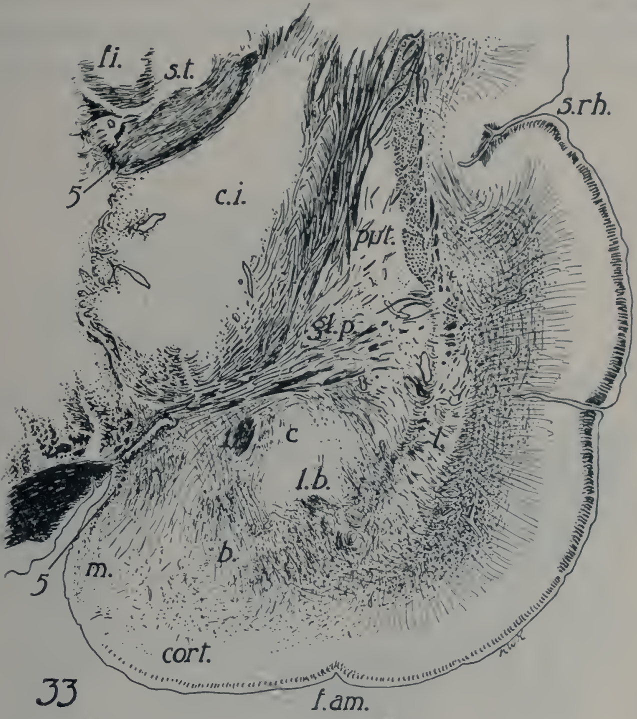


Fig. 33 Section 0.975 mm. forward from the last. In this figure and the next are seen the bundles of fibers coming out of the amygdala and pyriform cortex to connect with the stria terminalis and to go forward beneath the internal capsule and anterior commissure. They are seen especially traversing the basal nucleus and associated with the longitudinal bundle (*l.b.*). The commissural bundle is now very conspicuous. The stria medullaris bundle (*5*) separates from the optic tract and enters the amygdala. This figure falls between the levels of figures 55 and 56.

the optic tract and go forward among the superficial fibers of the medial forebrain bundle just medial to the entire pyriform-amygdaloid region. Here the fibers pass the medial border of the nucleus of the lateral olfactory tract and in transverse sections they seem to turn laterad and spread over this nucleus just beneath the superficial fiber layer derived from the lateral olfactory tract (fig. 35). In sagittal sections it is evident that a part

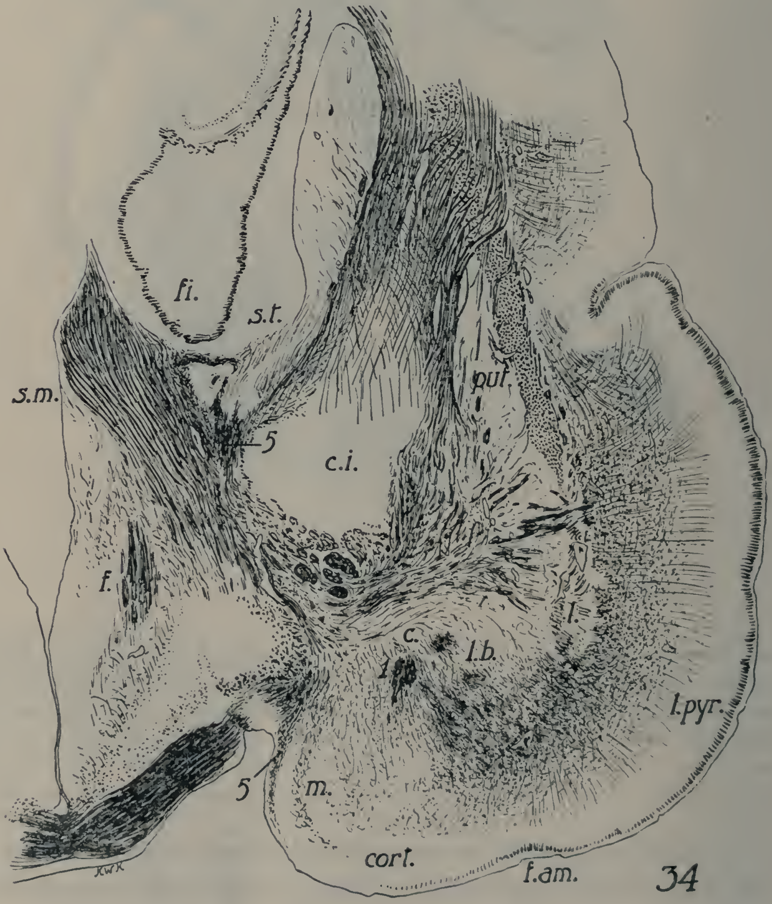


Fig. 34 Section near the anterior end of the amygdala, 0.375 mm. forward from the last. Note the connection of bundle *5* with the stria medullaris in the thalamus. Compare with figure 56.

of the stria medullaris fibers go on forward into the tuberculum olfactorium. The stria medullaris therefore has four connections (places of origin?) in the temporal pole: the pyriform cortex, the nucleus of the lateral olfactory tract, the tuberculum olfactorium and the hippocampus. The first three of these bundles are probably represented in fishes by the tractus olfacto-habenularis

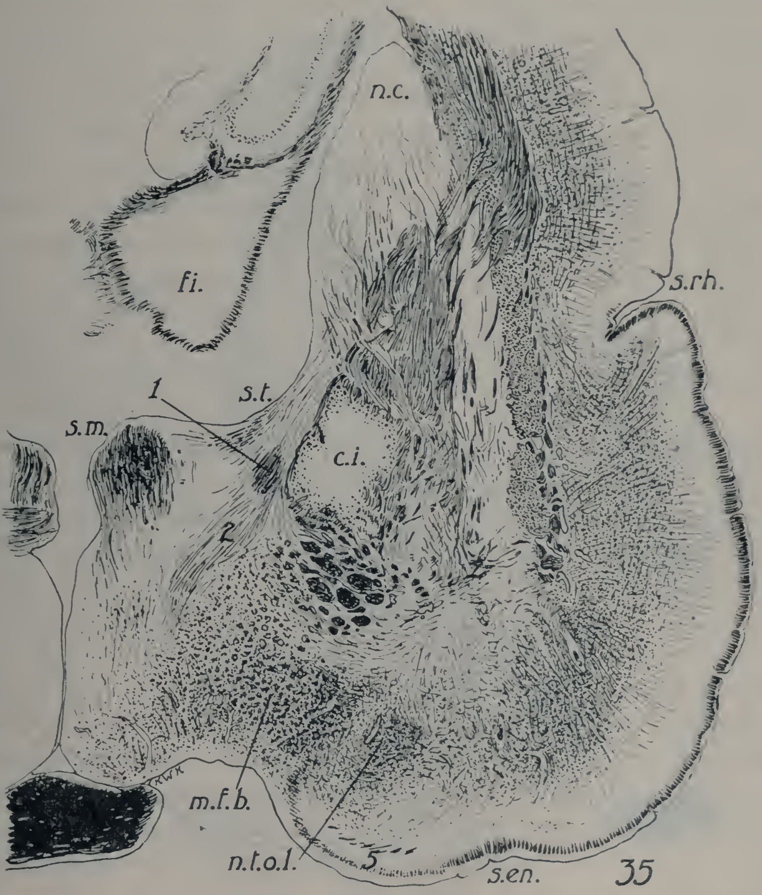
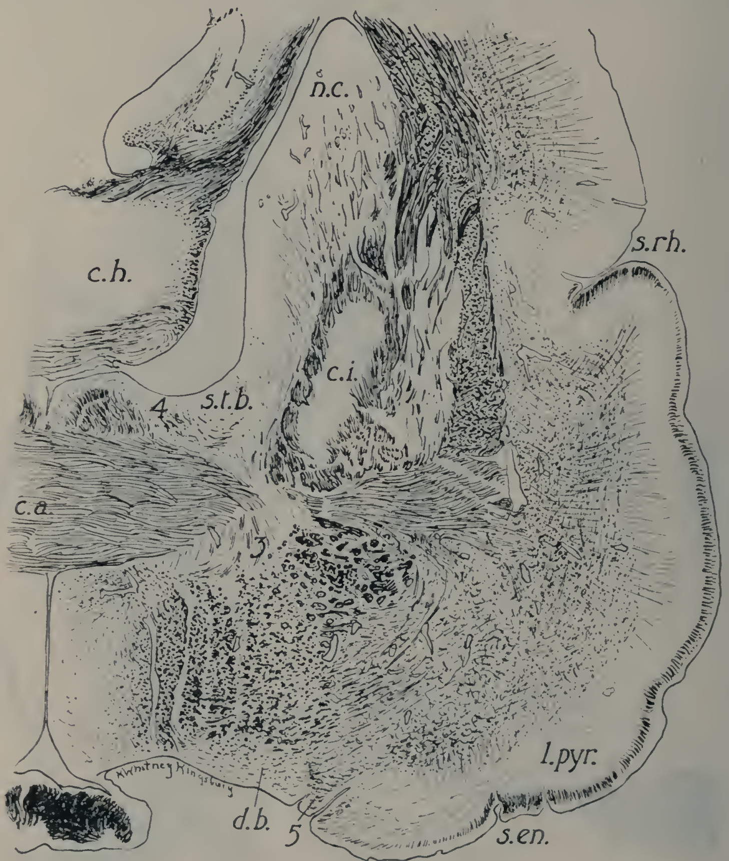


Fig. 35 Section through the optic chiasma, 0.825mm. forward from the last. The stria terminalis is shown in its enlarged bed above and behind the anterior commissure. The olfactory projection tract crosses in front of the stria medullaris of figure 34. The section cuts the nucleus of the lateral olfactory tract. Beneath the fibers of that tract appear the fibers of the stria medullaris bundle (*5*). Internal to those is the dense network of the terminations of the commissural bundle. Compare with figures 57 and 58.

lateralis and the last by the posterior pallial commissure or tractus corticohabenularis or both (Johnston, '11 a, p. 34, '11 b, p. 521).

The nuclei of the amygdaloid complex mentioned above by names indicating their position will be described in the following section.



36

Fig. 36 Section through the anterior commissure, 0.75 mm. forward from the last. Bundle *3* of the stria passes forward beneath the commissure, bundle *4* above it. In this and previous figures note the passage of internal capsule bundles through the putamen and the ending of such fibers in the caudate nucleus. Compare with figure 59.

In the rabbit the disposition of the bundles in the region of the anterior commissure closely resembles that in the opossum. The commissural bundle is much smaller in the rabbit. The supra-commissural bundle is large and shows several separate fascicles. These run farther forward than in the opossum and transverse sections give the impression that more fibers in the rabbit end in the parolfactory region. Caudally the bundles to the medial and central nuclei are the largest, the commissural and stria medullaris bundles and the bundles to the basal nuclei behave as in the opossum. Not many medullated fibers seem to go to the lateral nucleus. My rabbit preparations are not suitable for a more detailed analysis of the fibers.

Human foetal brains prepared with ordinary histological stains are of course unsuitable for the study of the fiber tracts in detail. In the region of the anterior commissure only the infra- and supra-commissural and the hypothalamic bundles can be recognized. In the amygdaloid complex the distribution of the stria to the several nuclei is clearly of the same type as that seen in the opossum and the rabbit.

In the turtle the following bundles have been described (Johnston, '15 b): First, a commissural bundle related to the small-celled nucleus, which was described as continuous with or as including the nucleus of the lateral olfactory tract; second, a broad bundle surrounding the commissural bundle and connecting the chief (small-celled) amygdaloid nucleus with the parolfactory area. Its fibers pass both above and below the anterior commissure. Third, an olfactory projection tract likewise arising from the small-celled nucleus and running to the hypothalamus. Fourth, a non-medullated bundle arising from the large-celled medial nucleus, whose destination was not made out.

In the frog Herrick ('21) recognizes a stria terminalis connecting the amygdala with the medial olfactory area.

4. THE AMYGDALOID COMPLEX

a. General. The amygdaloid fissure

The history of the bed of the stria terminalis treated in a previous section shows that a primary relation exists between at least part of the amygdaloid complex and the olfactory apparatus.

Although the gray accompanying the stria in adult man and mammals is small in volume, there are throughout its length scattered nerve cells representing the vestiges of a gray mass which in the embryo and in lower vertebrates was continuous with the olfactory nuclei in front. In fish-like vertebrates (except Dipnoi?) there is no amygdala separated from these olfactory nuclei. In reptiles, as explained in previous papers ('15 b, p. 428, figs. 59, 60; also '16 b) the hemisphere has enlarged and elongated, the olfactory area has spread caudad until it covered the striatal area, and finally the thickening of the internal capsule has caused the striatum to bulge laterally and the olfactory centers have withdrawn to its borders. The thickening of the internal capsule, taking place between the anterior and posterior parts of the olfactory centers, has caused the ventricular olfactory layer or area to arch up in the middle. This layer contains in the turtle the fiber tracts above enumerated, two of which (the commissural and the hypothalamic bundles) are known to be present in fishes. These bundles constitute the stria terminalis and the elongated and arched gray mass in which they lie is simply a part of the primitive olfactory centers. The further thickening of the internal capsule in mammals has brought about the reduction of this gray in the middle of the arch to a small but significant vestige, the bed of the stria terminalis. The anterior end remains in the medial part of the head of the caudate and the nucleus accumbens. The caudal part remains as important nuclei in the medial part of the amygdaloid complex, now to be described.

The central nucleus. In reptiles this clearly forms the largest and most centrally located part of the amygdaloid complex and it is described first because in mammals it is central also in the sense of being the oldest part around which the other members of the complex come to be grouped. In the turtle ('15 b) the area in the floor of the lateral ventricle which I formerly called the nucleus caudatus and which in this paper is called the bed of the stria terminalis, in the temporal lobe enters into a large area of small cells the outer portion of which is the nucleus of the lateral olfactory tract (fig. 17). The whole area is small-celled and is to be interpreted as the caudal end of the olfactory centers in which the superficial nucleus of the lateral olfactory tract remains in continuity with the ventricular layer. In mammals the deep part of this area becomes separated from the nucleus of the lateral olfactory tract by the development of new gray masses, and appears as the caudal enlarged end of the bed of the stria terminalis. In the turtle this common area of small cells is connected by broad fiber tracts with the parolfactory area and with the hypothalamus. The nucleus of the lateral olfactory tract also gives rise to the commissural bundle.

When the amygdaloid enlargement of the bed of the stria terminalis is examined in mammals it is found to be incompletely divided into two parts. The medial portion becomes expanded into a vertical plate occupying the medial wall of the temporal lobe immediately adjacent to the sulcus hemisphericus and rostral to the temporal horn of the ventricle (figs. 54, 69, 77, 83, 84, 99). The medial portion of the stria terminalis, as already described, descends directly into this mass. It should be called the medial amygdaloid nucleus. In view of the mammalian homologies the nucleus in the turtle brain heretofore called the medial nucleus is better called the basal nucleus (see below).

Immediately lateral to the medial nucleus the remainder of the small-celled area forms a large central nucleus which borders upon the globus pallidus, the tail of the caudate nucleus and the caudal part of the putamen. It extends forward to the level of the anterior commissure where it comes into relation with the deep gray of the broad caudal end of the diagonal band where it covers the whole width of the brain base from the thalamus to the external capsule. Here the diagonal band merges with the central amygdaloid nucleus. This central nucleus is thus the largest of the amygdaloid nuclei and its shape varies in different orders as it accommodates itself to surrounding structures. There appear to be certain subdivisions of this nucleus into somewhat separate clumps or masses of cells. Some of these are dense, deeply stained wedge-shaped or triangular masses, others rounded or ovoid clumps imbedded in the general mass (figs. 55, 71, 85, 98, 99). Some of these may be products of the infolding to be described below. Otherwise I do not attach any significance to them. This central nucleus gives origin to most of the fibers of the hypothalamic bundle as described in the opossum. This is the olfactory projection tract of Cajal.

The amygdaloid fissure. In order to understand the other amygdaloid nuclei it is necessary to examine carefully their mode of formation. The key to this is found in the amygdaloid fissure described by the writer in the turtle ('15 b). An understanding of this fissure and the part it plays in the evolution of the amygdaloid complex is of the utmost importance and this will justify a detailed examination of its relations. The description first given implied that the whole dorsal ventricular ridge was derived from an infolding in the amygdaloid region. In a later paper ('16 b) it was shown that the dorsal ventricular ridge is formed by an infolding along the lateral border of the general pallium. In a preliminary notice ('18) and in the present paper it has been shown that this ridge becomes the caudate nucleus, which arises in the same way in the mammalian brain. In the adult brain of the turtle ('15 b, figs. 4, 10) the caudal part of the ridge projecting into the ventricle is separated from the rostral part by a prolongation of the middle ventricular groove which bounds the dorsal ventricular ridge ventrally. In the embryonic stages studied there was no indication of a separate mass being formed in this region. Probably the embryos studied were not advanced enough to give a complete history of these ridges. There is abundant other evidence that the caudal part is morphologically and functionally different from the rostral part. The caudal part is related to the amygdaloid complex as at first supposed, the rostral part forms the caudate nucleus.

The evidence of morphological independence is found in the mode of origin of the two ridges (or two parts of what appears to be one ridge in the turtle). The rostral part is formed by rapid proliferation of neuroblasts, growth and bulging inward of the lateral border of the general pallium. This takes place above the sulcus rhinalis which marks the dorsal border of the lateral olfactory area or pyriform lobe. The caudal part is formed by a more pronounced infolding of the ventral wall of the temporal pole along the line of the sulcus endorhinalis. This sulcus, as is well known, lies wholly within the lateral olfactory area. At the level of the nucleus of the lateral olfactory tract, the in-wandering of cells and the external groove which marks it lie between the nucleus of the lateral olfactory tract and the pyriform lobe. Since there exist here an external groove and a corresponding internal ridge and since there is evident in some animals an actual folding of the wall, it may be said that the temporal portion of the sulcus endorhinalis is transformed into a true fissure. The internal ridge or thickening enters into the amygdaloid complex and I have therefore called this the amygdaloid fissure. This fissure is marked by a large external groove in the turtle (figs. 17, 18) and in all mammals studied by a less conspicuous groove. It is shown in figures 52 to 56, 68 to 77, 83, 84, 85. In human embryos and foetuses the fissure is crowded somewhat more toward the medial surface of the temporal lobe but is clearly evident.

The internal ridge in the reptilian brain corresponding to the amygdaloid fissure has been more or less clearly recognized as a body of special significance by earlier authors. C. L. Herrick ('91, '93) called attention to it under the name of occipito-basal lobe. Adolf Meyer ('92) calls this the nucleus sphaericus and describes it as pushing into the caudal end of the long dorsal ridge which he calls lateral ganglion. Edinger ('96) first used the name epistriatum for this body and later applied the same name to various other structures. Kappers ('08) calls the dorsal ventricular ridge 'epistriatum' and the body in the temporal pole 'secondary epistriatum.' From his description of the fiber tracts it does not appear that the two bodies were clearly distinguished. De Lange ('11) in one series of figures of Varanus calls the rostral part of the ridge 'striatum' and the caudal part 'epistriatum' in which the nucleus sphaericus is imbedded. In a second series of figures he applies the name epistriatum to the whole length of the ridge. He describes a connection of the cells in the dorsal part of the ridge with the cortex, but says that the greater part is filled with cells of striatal type. He considers that the whole structure has a striatal character and is derived from the striatum, having attained a secondary connection with the cortex. In Lacertilia and Ophidia the caudal part (that which is related to my amygdaloid fissure) is much larger than in Chelonia and de Lange has made reconstructions and dissections of Eunectes and Varanus which show this. In these forms he finds a large rostral ridge which receives fiber bundles coming up from the sensory centers of the thalamus. This ridge he calls the 'neostriatum,' while for the caudal ridge he retains the name epistriatum. Through an unaccountable failure to correctly follow the same thalamic tracts in Chelone, de Lange fails to see that the neostriatum of Varanus is the same as the rostral part of his epistriatum in Chelone. In Chelone he applies the term neostriatum to the body in which the stria terminalis is imbedded. In other words, de Lange's neostriatum of figures 45, 46 and 47 is the epistriatum of figure 44, while the neostriatum of figure 44 is the bed of the stria terminalis. When de Lange points out that the neostriatum far forward reaches beneath the ventricle into the medial wall to form the 'nucleus accumbens septi,' this statement can be true only for what he calls neostriatum in Chelone and not at all for the neostriatum of Varanus or Eunectes. The essential explanation of the confusion in the terms of de Lange and others is that the dorsal ventricular ridge of the turtle (not including the ridge formed from the amygdaloid fissure) extends far back in the turtle and is separated from the amygdaloid ridge by a shallow ventricular groove. This ridge is shorter in Varanus and Eunectes and is called by de Lange neostriatum The amygdaloid ridge in these forms is much larger than in turtles and extends far forward in the ventricle. When de Lange insists that the nucleus amygdalæ of mammals is homologous with the epistriatum he is right in so far that some part of his epistriatum enters into the amygdaloid complex of mammals, but there remains the unfortunate confusion as to what is included in the 'epistriatum.' His proposal that the amygdala of mammals be called 'archistriatum' has no foundation, since the amygdala has nothing whatever to do with the striatum at any time.

In my first study of the turtle brain ('15 b) I gained the impression that the whole of the dorsal ventricular ridge was derived from the infolding at the amygdaloid fissure, while the body known to different authors as occipito-basal lobe, nucleus sphaericus or epistriatum owed its origin to the hypertrophy of the small-celled nucleus related to the bed of the stria terminalis and the nucleus of the lateral olfactory tract. "In the lizard this mass is greatly enlarged and forms a prominent lobe or ridge in the ventricle" (p. 414). "This ventricular ridge is a wholly different structure from the 'epistriatum' of Kappers" (p. 418). Both these statements were erroneous and only added to the confusion. The later study of the development of the dorsal ventricular ridge ('16 b) showed that it was derived from the lateral border of the pallium and that it was destined to form the caudate nucleus. What that study did not show is that the caudal ridge which is incompletely separated in the turtle has a wholly different origin, namely from the amygdaloid fissure.

There are in reptiles a rostral and a caudal ridge in the lateral hemisphere wall, which form sharply marked independent eminences in lizards and snakes but in turtles are separated only by a shallow groove. The rostral ridge is derived from the general pallium and forms the caudate in mammals. The caudal ridge is formed from the amygdaloid fissure and enters into the amygdaloid complex in mammals.

Miss Crosby ('17), in studying the forebrain of the alligator, follows closely the interpretation given by the writer in describing the turtle brain. She does point out that the anterior part of her 'dorso-lateral area' (my dorsal ventricular ridge) is concerned more largely with somatic sensory fibers while the caudal part receives olfactory fibers. The condition in the alligator seems to be intermediate between that in the turtles and the lizards without a very clear separation of somatic and olfactory regions.

Elliot Smith has recently reviewed ('19) the work of various authors in a way that might have cleared up the whole matter if he had been acquainted with the distinctness of these rostral and caudal ridges. Whereas Kappers, de Lange and others partly distinguish and partly confuse the two parts of their 'epistriatum,' Smith emphatically insists upon the unity of the entire length of the ridges projecting into the ventricle. "The first point which I want to emphasize is that the whole of the hypopallial eminence, its extent not merely in the transverse plane (fig. 1,

H^1 to H^5), but also in the longitudinal direction—from the extreme anterior end to the postero-inferior recess of the hemisphere (fig. 5, HP) is composed of pallium with a well-defined and unmistakable band of cortical cells."

Professor Smith was led to this conclusion by the connection of the cell layers of the ridge with cortical areas, but he has not sufficiently considered the character of the cortical areas with which the rostral and caudal parts of his 'hypopallium' are connected. In Smith's figure 5 his hypopallium is deeply notched over the stalk of the hemisphere. This notch together with the shallow groove running back from it across the ridge, both in Sphenodon and the turtle (see my figures for Cistudo and Smith's figure 14 for Chelone), corresponds to de Lange's sulcus strio-epistriaticus (his figure 46) and separates the rostral and caudal ridges.

The epistriatum of de Lange's figure 46 is the same as the *AM* of Smith's figure 14, but greatly hypertrophied. Now all of Smith's sections and those which he copies from de Lange and myself, except his own figure 10 of Sphenodon, have to do with the anterior region. His figure 10, although not sufficiently detailed for any certain conclusions, does suggest differences between the rostral and caudal parts of the ridge in Sphenodon.

Professor Smith makes no distinction between the different parts of the pallium to which his hypopallium is attached in Sphenodon. In interpreting my figures of the turtle brain the fact that the ventricular ridge is connected with the pallium above the lobus pyriformis in the rostral region and with the lower edge of the lobus pyriformis in the caudal region does not suggest that the kind of cortical area concerned would make some difference in the interpretation of the ridge itself.

In discussing Chelone, Smith does give separate treatment to the caudal ridge in the following words: "Posteriorly the hypopallial eminence is continuous with a less prominent and irregular mass (*AM*) which is attached by a broad base to the postero-ventral recess of the ventricle, the first rudiment of the inferior cornu. The constitution of this little mass (*AM*) is similar to that of the rest of the hypopallium, of which it is merely the caudal extremity. It represents the hypopallial element of the nucleus amygdalæ of mammals and is pallial in origin." In this he comes nearest to the true interpretation of this ridge. The only difficulties are that its constitution is not similar to that of "the rest of the hypopallium," that it is not merely the caudal extremity of the 'hypopallium,' that it represents a pyriform (not hypopallial) element in the amygdala of mammals while the structure derived from the rest of the 'hypopallium' has general pallial characters and relations and becomes the caudate nucleus. Smith states ('19, p. 286) that "the line along which the cortical band bends inward to form the hypopallium . . . corresponds to the endorhinal fissure . . . The infolding of the primordium neopallii, however, takes place above the anterior end of the area pyriformis corresponding to the line of the rhinal fissure." I showed clearly in the second of my papers to which Professor Smith refers ('16 b) that the hypopallium (dorsal ventricular ridge, caudate nucleus) is derived from the border of the general pallium above the area pyriformis corresponding to the rhinal fissure. At the caudal end of the endorhinal sulcus there is an infolding to form the ridge *AM* of Smith which becomes a part of the amygdaloid complex. It is important to understand that the ridge which gives rise to the caudate nucleus (anterior part of Smith's hypopallium) is much more closely related to the pallial thickening (motor pallium mihi, primordium neopallii of Crosby and Smith) than it is to the ridge which enters into the amygdaloid complex. Nevertheless these do not form a continuous or unified mass.

In another place (p. 288) Smith speaks of the area pyriformis being "in the midst of the area affected by these new influences," *i.e.*, thalamic fibers entering the pallium, and invokes Kappers' principle of neurobiotaxis to explain why it is not involved in the infolding. In fact, however, the area pyriformis is never in the midst of the pallial area but arises in the ontogeny and remains latero-ventral to the pallium and to the line of infolding of the pallium which forms the caudate nucleus. Here it maintains its direct relation to the lateral olfactory tract.

In a strange mixture of invective, misquotation and criticism published by Dart ('20) there is a recognition of an anterior and a posterior hypopallium. The posterior portion alone is treated as an element of the amygdala. "The anterior portion is the goal of the afferent system from the thalamus, the posterior region discharges by a tract which runs at any rate for the most part to the habenula." Dart, however, seems to derive the whole of his hypopallium from the hypertrophy of the area pyriformis. This is clearly stated by Shellshear ('20, p. 30). One could wish that Dart's paper had contained more description and less wrangling, as further contributions of fact on this subject from Professor Smith's laboratory would be welcome.

While I cannot give an account of the development of the posterior part of the ridge (the ridge *AM* of Smith's figure 14) because it takes place in later stages than those I possess, the relations of the amygdaloid fissure in the opossum, rabbit, bat, bear, monkey and numerous stages of human foetal brain show that it is a very different structure. In all forms just mentioned the amygdaloid fissure lies within the lateral olfactory area in the primitive sense of that term. More specifically, it lies between the pyriform cortex laterally and the nucleus of the olfactory tract medially, and the external groove is traversed by a part of the lateral olfactory tract which is being distributed to that part of the pyriform lobe which extends beyond the fissure caudally. A re-examination of the turtle brain in Golgi sections made since the 1915 and 1916 papers were written convinces me that I assigned too large a part of the temporal pole to the general pallium. The fibers of the lateral olfactory tract passing by the nucleus of that tract run round the ventro-caudal angle into the caudal surface of the temporal pole. This area must therefore be regarded as pyriform lobe. The cortex here is of a simple, unspecialized character and blends with the nucleus of the lateral olfactory tract. In figures 5, 8, 9 of the 1915 paper the forked area of general pallium surrounding the fissura amygdalæ should be represented as pyriform lobe lateral and caudal to the fissure and as amygdaloid complex between the fissure and the hippocampus. Likewise in figures 12, 13, 14, 15 the areas lateral to the fissura amygdalæ labeled *g.p.* should be assigned to the pyriform lobe and that medial to the fissure should be assigned to the amygdaloid complex (comparable to the cortical nucleus in mammals).

The infolding which takes place here gives rise to a large part of the amygdaloid complex in mammals. In the turtle the relations of this infolding to the dorsal ventricular ridge can be explained only on the supposition that after the latest stage of development described in my 1916 paper the amygdaloid ridge pushes in and displaces the pallial derivative forward, thus giving rise to what I have been calling the caudal portion of the dorsal ventricular ridge. The true nature of this can be determined only by a study of its fiber connections. These will be described in the following sections so far as the facts are available. The purpose of the foregoing discussion has been to show that there enter into the mammalian amygdaloid complex elements which are derived from an infolding in the pyriform area, an infolding which is present in varying size in the reptiles and has there been confused with the infolding from the general pallium which gives rise to the caudate nucleus in mammals.

It may help to clarify the whole matter if the statement quoted from Elliot Smith on page 342 as to the fate of his hypopallium be rewritten thus: The hypopallium of reptiles consists of two distinct parts, both of which persist in the mammalian brain. The rostral portion, derived from the general pallium, forms the tail and part of the head of the caudate nucleus. The putamen and globus pallidus of the lenticular nucleus are derivatives of the palæostriatum. The palæostriatum also gives rise to part of the head of the caudate and the adjacent nucleus accumbens both of which are continuous with an elongated column of gray parallel with the caudate nucleus and forming the bed of the stria terminalis. The caudal part of the hypopallium (Smith), derived by infolding from the area pyriformis, enters into the constitution of the amygdaloid complex along with the caudal part of the bed of the stria terminalis and other structures.

The basal nuclei. These are a part of the product of the infolding at the amygdaloid fissure. In the turtle the only part of this mass which represents a specialization in the character of its cells or its fiber tracts is the medial portion which was previously called the medial nucleus. This is a group of cells much larger than those of the nucleus of the lateral olfactory tract, lying in the medial part of the amygdaloid ridge lateral to the temporal horn of the ventricle. From this nucleus a compact bundle of non-medullated fibers runs forward quite isolated from other stria bundles, to join these at the caudal border of the internal capsule. The destination of this bundle has not yet been made out.

It is clear that we have here a special amygdaloid nucleus and the following description will show that its homologue can be identified in mammals. Miss Crosby ('17) compared with this her nucleus ventro-medialis in the alligator. This, however, differs in two marked respects from the nucleus medialis of the turtle. The nucleus ventro-medialis in the alligator is composed of small cells like those of the nucleus of the lateral olfactory tract and Miss Crosby states that it gives rise to part of the stria medullaris and to the olfactory projection tract of Cajal, while the nucleus medialis of the turtle is large-celled and does not give rise to the olfactory projection tract. The position assigned to the nucleus ventro-medialis in Crosby's figure 12 corresponds to that of the medial nucleus in the turtle, but farther forward (figs. 9, 18, 21) this nucleus seems to merge with the nucleus of the diagonal band. It seems probable that the medial nucleus is not developed as a special nucleus in the alligator, or that it lies farther dorsally in the amygdaloid ridge.

Herrick ('21) has compared the medial nucleus of the turtle with the amygdala described by him in the frog. But this appears from his description to correspond rather to the whole small-celled area in the turtle including the nucleus of the lateral olfactory tract and the caudal end of the bed of the stria terminalis (see below, p. 464 to 467).

When the brains of marsupials and mammals are studied we find that the expansion of the hemisphere has first in the marsupial produced a broader temporal pole and allowed the amygdaloid complex to spread and flatten out somewhat (figs. 53, 54) and then in mammals has carried the caudal wall of the hemisphere around beneath the temporal pole so that for some distance the amygdaloid complex in human foetal brains seems to occupy the roof of the temporal horn of the ventricle. In all these forms there are to be found in addition to the structures recognized in the turtle two or three distinct areas or cell-masses which owe their origin to further immigration of cells and differentiation in the region of the amygdaloid fissure.

b. The amygdala of the opossum

As one follows a series of transverse sections from behind forward the first part of the amygdaloid complex to appear is a plate of cells under the temporal horn of the ventricle and separated from the ventricle by the deep fiber layer (external capsule) which is continuous with the corona radiata (figs. 29, 52). In this plate are seen many dense clumps or clusters of cells which remind one of the islands of Calleja in the tuberculum olfactorium. The outer surface opposite this cell-plate is marked by a slight groove in which the fiber layer formed by the lateral olfactory tract is slightly thickened. This groove is the amygdaloid fissure and is continuous forward with the sulcus endorhinalis. The layer of olfactory tract fibers covers the whole surface from a point near the medio-ventral angle (hippocampus) to the sulcus rhinalis on the lateral surface. As the new cell plate is continued forward it is particularly important to notice that it is separated from the ventricle by the external capsule and that outside of this nucleus is a fairly dense network of fibers from which rise the radiating fibers of the pyriform cortex. The new nucleus seems to be imbedded in or to intrude into the deep layer of radiating fibers of the pyriform cortex. This plate of cells is not found as a separate nucleus in mammals. I, therefore, propose for it the name accessory basal nucleus.

A short distance farther forward two other gray masses appear. Medial to the nucleus just described the brain wall is thickened by a rapidly increasing number of cells without regular arrangement. These cells form an indistinct amygdaloid nucleus which in the opossum remains covered by a cortical layer similar to the pyriform cortex. These two adjacent cortical areas are separated by the break and in-bending at the amygdaloid fissure. In mammals the cortical arrangement of cells is lost over more or less of this area medial to the fissure. I am, therefore, inclined to think that both the superficial cells and those which have migrated deeper form a functional unit which I shall call the nucleus corticalis. Lateral to the accessory nucleus appears a new mass very sharply separated from it. This body lies on the ventricular side of the corona radiata and is at first triangular in cross-section, being bounded on two sides by the corona radiata and on the third by the ventricle. At the level of figures 30 and 53 the three bodies lie side by side forming an extensive semilunar mass lying in the concavity of the pyriform lobe. The most lateral of the three bodies seems at this level to be devoid of myelinated fibers. It is the lateral amygdaloid nucleus.

Not far forward from this (figs. 31, 54) very significant changes have taken place. Dorsal to the cortical nucleus has appeared a large-celled nucleus (*nuc. am. b.*). It is the basal nucleus and corresponds to the large-celled nucleus in the turtle which was called medial nucleus ('15 b). Medial to this nucleus the extreme medial angle or convexity of the brain wall is occupied by the medial nucleus described above. It is composed of small cells which come together in a dense layer continuous with the cortex of the pyriform lobe. Lateral to this and directly beneath the ventricle is the beginning of the central nucleus. Note that the medial and central nuclei are intimately related and that these are the two nuclei into which the bed of the stria terminalis seems to expand. The accessory basal nucleus and the lateral nucleus occupy the space lateral to the amygdaloid fissure. Now on the internal surface of the lateral nucleus rests the tail of the caudate nucleus which curves about the corona radiata somewhat in the form of a boot (fig. 54). Between the caudate nucleus and the central nucleus lies a thin dense plate of cells which a little farther back fuses with the central nucleus. This is a continuous plate of cells which appears in all following sections up to the anterior commissure. It is called the intercalated mass.

Going back now to the fiber bundles related to these masses, we see in figures 30 and 31 that the external capsule comes down outside of the lateral nucleus and at the lateral border of the accessory basal nucleus divides into an outer network lying between the amygdaloid nuclei and the pyriform cortex and a deep layer of longitudinal fibers which run between the lateral and the basal nuclei. The fibers between the lateral and basal nuclei are of two categories. A large part of them are external capsule fibers turning into the amygdaloid nuclei. Since the external capsule here contains fibers from olfactory nuclei, from the anterior commissure, from the corona radiata, association fibers connecting the pyriform lobe with the general cortex and many intrinsic fibers of the pyriform lobe itself, it is impossible to say what kind of fibers enter or leave the amygdaloid complex through this channel. It is evident that there is abundant opportunity for amygdalo-pyriform connections and also for connection with the general cortex and even lower centers by way of the corona radiata and internal capsule. The writer believes that at least fibers from olfactory nuclei, the anterior commissure and pyriform lobe play an important part here.

The other fibers contributing to these longitudinal bundles come from the stria terminalis. Their relations are shown in figures 21, 26, 27, 31, 32, 34. The fibers in question are the more lateral ones destined chiefly to the accessory basal nucleus and belonging to the bundle *4* of the diagram already discussed (fig. 20).

Medial to these bundles and lying as a flattened layer immediately beneath the ventricle is the bundle *3* which is destined to the basal and the cortical nuclei. When the medial and central nuclei appear in section (figs. 30, 54), the large fine-fibered bundle *2* comes down close over the internal capsule and spreads out in these. When the caudate appears in section its surface is covered by a thin ventricular layer of fibers longitudinal in direction. These form a thin layer of myelinated fibers between the tail of the caudate nucleus and the lateral amygdaloid nucleus (fig. 31). The significance of these fibers is not clear. The lateral nucleus now appears to be penetrated to some extent by myelinated fibers chiefly derived from the external capsule or pyriform lobe.

Passing on forward (figs. 32, 55) the amygdala comes to lie beneath the internal capsule and the temporal ventricle disappears. The medial nucleus continues and is a little larger than in figure 54. The central nucleus has greatly enlarged. Lateral to it lies the globus pallidus-putamen. The caudate has fused with the putamen since the last section studied. There is no very sharp boundary between the central and the lentiform nuclei, but in Weigert sections (fig. 33) the fibers radiating from the internal capsule through the globus pallidus show fairly well the location of the latter. There may easily be and probably are associative and correlating connections between the lentiformis and amygdala here; but there is no intimate fusion of the two and there is no evidence that the putamen enters into the formation of the amygdala. The putamen is distinctly richer in myelinated fiber network than the central amydgaloid nucleus. The basal large-celled nucleus is now conspicuous and an important layer of fibers between it and the central nucleus derived from bundle *3* of the stria terminalis extends on forward to supply the basal nucleus. The lateral nucleus is nearly a rectangular body and the accessory nucleus is reduced to a small mass near the amygdaloid fissure.

At the region of the accessory nucleus where so many fibers come into the amygdala from the pyriform lobe and external capsule there is formed a prominent dense bundle cut across in section (fig. 30). This bundle continues for a long distance forward and backward and seems to be composed of fibers connecting the amygdala and the pyriform lobe. Farther forward we shall find a special slip from bundle *2* of the stria terminalis entering this bundle. This slip, however, would form only a smaller part of the bundle in question and since this bundle dwindles away both in front and behind I conclude that this is an amygdala-pyriform association or correlating bundle. It probably contains fibers arising in various parts of the pyriform lobe and ending in various nuclei of the amygdala and other fibers arising in the amygdala and going to the pyriform lobe. It is the 'sagittales Längsbundel' of early authors, but is independent of the bundle connected with the nucleus of the lateral olfactory tract, to which this name has sometimes been applied.

In sagittal sections (figs. 21, 26, 27) this bundle appears more diffuse than in this transverse series. I attribute this to a variation in individuals. The connection of bundle *2* with this longitudinal bundle is seen in figures 26 and 27. There is some indication also of fibers from this region passing forward in the diffuse network beneath the anterior commissure, a condition first seen in man and the monkey (see below).

In all the sections thus far described the amygdaloid fissure has been marked not only by the external groove but by a sharp break in the cortex of the pyriform lobe. The cortical layers turn inward and from the free edges cells seem to be migrating toward the deep nuclei. The actual migrating of cells presumably ended with foetal development, but the shape and grouping of the cells even in the adult gives a picture of the end stages in the formation of those parts of the amygdaloid complex which owe their origin to this infolding and immigration of cells. The medial and central nuclei are distant from the fissure and show no relation to it. The basal nucleus with its large cells also seems to have no close relation to the fissure in the opossum. The cortical nucleus and the lateral nucleus, however, appear to owe their formation to the immigration of cells from the region of the fissure. The cortical nucleus is composed of small cells like those of the nucleus of the lateral olfactory tract and has been the least displaced by the infolding. It may be regarded as a relatively primitive part of the amygdala whose cells have moved inward and medialward as new nuclei were forming by infolding. The indication that cells migrate into it from the fissure is seen in figures 55 and 56.

In the caudal part of the amygdala where the accessory basal nucleus is most strongly developed, this is the cell mass most closely related to the fissure. However it does not appear that cells were migrating into this nucleus in late stages of development. One of the structural characteristics of this nucleus suggests that it is formed early in embryonic development. The dense clusters of cells scattered through this nucleus may be explained on the supposition that the nucleus was formed by either a mass movement or migration of cells at a stage before the multiplication mitoses of the germinal cells were completed, so that many cells were carried into it before they were differentiated into neuroblasts or glia elements. As the germinal cells went on to complete their multiplication the neuroblasts formed from them were situated in a deep mass crowded between older structures and there was very restricted opportunity for free movement. Hence the neuroblasts formed from one or more germinal cells remained clustered closely together in the midst of irregularly scattered cells whose multiplication had been completed before their migration.

The large lateral nucleus appears upon cursory observation to be least intimately related to the other parts of the amygdala. It is not penetrated by myelinated fibers in its caudal part, it does not seem to share in the distribution of stria terminalis bundles, it is separated from the basal nuclei by lying above, internal, to the external capsule while the basal nuclei are external to the capsule. In sections through the anterior part of the amygdala (figs. 55, 56) there is a very evident strand of cells leading from the amygdaloid fissure to the lateral nucleus. Apparently this was the last nucleus to be formed and this was the largest and most active migration of cells. Wandering cells from this region moved upward (inward) and backward between the developing external capsule and the putamen and pushed back until they formed a large body on the ventricular surface internal to the external capsule. At its caudal end this intruding body displaced the phylogenetically (and possibly ontogenetically) older fiber systems relating the amygdala and the pyriform lobe, and we see these connections passing behind or beneath the lateral nucleus and it is left deprived of myelinated tracts. Farther forward, however, it is crossed by fiber bundles connecting the putamen and pyriform lobe. The lateral nucleus ends just behind the point where the temporal limb of the anterior commissure enters the external capsule. Here it is a thin plate of cells extending up from the amygdaloid fissure along the inner face of the external capsule, and somewhat broken up into clumps or clusters of cells which take stain deeply.

The only fibers related to the lateral nucleus clearly seen in

Weigert preparations in the opossum are: piercing fibers from the internal capsule to the corona radiata, fibers between the putamen and pyriform lobe, fibers from the pyriform lobe ending in the lateral nucleus, and fibers of the anterior commissure which cross the anterior border of the lateral nucleus and run back in the external capsule along its outer surface. Many of these commissural fibers seem to enter the lateral nucleus. Anterior to the level just described the basal and cortical nuclei soon disappear from the sections. The central and medial nuclei continue (figs. 56, 57, 58) to the level of the nucleus of the lateral olfactory tract and all three enter into relation with the gray of the diagonal band.

The nucleus of the lateral olfactory tract gradually takes the place of the medial nucleus in the extreme medial angle of the temporal pole (figs. 57, 58). The central nucleus occupies the space between this and the anterior commissure and globus pallidus. The commissural bundle of the stria terminalis as already described, after being closely applied to the caudal surface of the internal capsule, runs forward and inclines downward (figs. 25, 33, 34, 35) until it reaches this nucleus. Here it enters into a rich network of fibers in the deep or central part of the nucleus, from which fibers radiate to all parts of the hemispherical cortex of the nucleus.

In sections through the anterior part of the medial nucleus and behind the nucleus of the lateral olfactory tract, the rich network of fibers in the pyriform lobe sends two broad sheets of fibers inward (figs. 33, 34). One of these comes from the medial border of the pyriform lobe and joins the network related to the amygdalo-pyriform association bundle in the basal amygdaloid nuclei. From this network many fine fibers converge into two fascicles close to the commissural bundle. These fascicles bend backward and unite with the large bundle of fine fibers which accompany the commissural bundle throughout its course. This is bundle *2* of the stria terminalis which runs to the hypothalamus. Here at the anterior end of the amygdala this hypothalamic bundle is related to the basal nuclei and pyriform lobe in addition to the medial and central nuclei. This division of bundle *2* does not end immediately in this network, but a large part of it turns into the amygdalo-pyriform association bundle in which it runs backward and presumably is distributed to the basal nuclei or pyriform lobe or both through the greater part of their length.

The second outflow of fibers from the pyriform lobe takes place beneath the putamen and consists of many bundles which converge into the temporal limb of the anterior commissure. The relations of the anterior commissure will be reviewed later. It is to be noted here that the anterior commissure bundles running back in the external capsule lie on the outer face of the lateral amygdaloid nucleus and may be in part distributed to it. The network of fibers of the anterior end of the amygdala is so complex that one cannot tell to what extent if any the anterior commissure is related to the amygdaloid nuclei here.

Just as the level of the anterior commissure is reached the amygdala comes to an end. The lateral division of the medial forebrain bundle sweeps across the sections to continue forward in close relation to the pyriform lobe and tuberculum olfactorium. The medial division turns into the parolfactory area, a large part of it ascending as precommissural fibers to the hippocampal formation. On the basal surface of the brain the amygdaloid complex is continued forward by the diagonal band of Broca which follows the general trend of the medial division of the medial forebrain bundle.

The amygdaloid complex in the opossum consists of the following six nuclei: medial, central, basal (large-celled), accessory basal, lateral and cortical. In close relation with these is the nucleus of the lateral olfactory tract. With the exception of the medial nucleus the complex is covered everywhere by the pyriform lobe and the nucleus of the lateral olfactory tract, and these are supplied throughout their whole extent with lateral olfactory tract fibers. From the pyriform lobe myelinated fibers in great numbers pierce at least the lateral, basal and cortical nuclei. The medial and central nuclei represent part of the primitive olfactory centers and it may be assumed that they still receive olfactory impressions. Indeed, fibers of the lateral olfactory tract certainly reach the medial nucleus while the central nucleus lies for a long distance directly upon the amygdalo-pyriform association bundle and the fiber network from the pyriform lobe penetrates the central nucleus. It is also possible that olfactory impulses reach these nuclei by way of the diagonal band. It is clear to the writer that all parts of the amygdaloid complex in the opossum are brought under the influence of olfactory impressions, directly or indirectly. The large-celled basal nucleus perhaps receives the fewest olfactory impulses from the routes above mentioned. But the stria terminalis bundle (*3*) which supplies it comes from the parolfactory region and in all probability carries olfactory impulses to the amygdala, although it may also contain fibers carrying impulses from the medial nucleus to the parolfactory or hippocampal areas.

Other impulses entering the amygdaloid complex may come from the pyriform lobe, from the adjacent nuclei of the corpus striatum, or from lower centers through bundles of the stria terminalis. Impulses coming from the pyriform lobe are not simple olfactory impulses. Since the pyriform lobe has very large numbers of associating fibers connecting it with the adjacent general cortex along its whole lateral border, the impulses passing from the pyriform lobe to the amygdala have already come under the influence of the general pallium. Moreover, since the deep fiber layer of the pyriform lobe contains these association fibers from the general pallium it is possible that some of these fibers enter the amygdala directly—an hypothesis which can be tested only by experiment. For the greater part of its length the amygdala lies in direct contact dorsally with the tail of the caudate nucleus, the putamen or the globus pallidus and for a long distance the globus pallidus and putamen are deeply wedged in between the central and lateral nuclei. It would be very strange if there were not an active interchange of impressions between these primarily somatic nuclei of the striatum and the primarily olfactory nuclei of the amygdala.

Of the stria terminalis bundles those numbered *2* and *4* in figure 20 run to the hypothalamus and contain the fibers which carry the effective impulses from the amygdala to lower centers. Bundle *2* is clearly the olfactory projection tract of Cajal. If these bundles contain fibers which carry ascending impulses, these are probably gustatory impulses which in fishes are brought to the hypothalamus by large tracts from gustatory nuclei in the isthmus, as described by Herrick ('05) and the writer ('11 b). I have shown in earlier papers ('11 a, '11 b) that an important tract in fishes, the tractus pallii, probably carries gustatory impressions from the hypothalamus into the area in the forebrain which I have called primordium hippocampi. This tractus pallii runs on the outer surface of the brain, lateral to the optic tract and the lateral forebrain bundle. It is very obvious that in respect to the course followed no tract in the stria terminalis corresponds to the tractus pallii of fishes. Herrick ('21 b) states that "The dorsal olfactory projection tract is one of the oldest and most conservative fiber systems in the vertebrate brain, having long been known and described in various types of fishes under the name tractus pallii." I find two difficulties in the way of accepting this interpretation. The first is the difference in position of the tracts compared; the second is the fact that the tractus pallii is composed chiefly of ascending fibers which probably carry gustatory impulses. Fibers connecting the basal olfactory centers with the hypothalamus in fishes run sometimes in a large diffuse basal bundle, sometimes in medial and lateral parts related to the medial and lateral olfactory areas respectively, but always clearly distinct from the lateral forebrain bundle which consists of fibers corresponding to the thalamo-pallial radiations in higher forms. (Fibers clearly corresponding to the pyramidal tracts have not been described in fishes.) The fibers from the lateral olfactory centers to the hypothalamus take a course medial to the thalamic radiations such that when the olfactory nucleus is carried back into the caudal pole of the hemisphere this tract bends over the internal surface of the thalamic radiations (*i.e.*, internal capsule) in the form of a semicircle. This is the olfactory projection tract. It may carry the gustatory impressions in reptiles and mammals.

The tractus pallii is a very different matter, both in its morphological relations and in its phylogenetic significance, and the suggestion that it is the homologue of the olfactory projection tract is inadmissible. The tractus pallii runs on the lateral surface of the brain and if present in reptiles and mammals must be expected to slip through from the temporal pole of the hemisphere to the hypothalamus outside of and behind the internal capsule and crus and outside of or interlaced with the optic tract, not around the ventricular surface of the internal capsule in the course taken by the olfactory projection tract. No such tract has been found in reptiles or mammals and it is scarcely to be expected.[2] The tractus pallii is found in fishes in which—including selachians—the gustatory apparatus is vastly more important relative to other structures entering into the diencephalon and telencephalon than it is in mammals or even reptiles. It is probable that gustatory impressions in fishes go up to the forebrain in both the tractus olfacto-hypothalamicus and the tractus pallii. The tractus pallii entered into that area which was developing into the hippocampal formation and the demand for correlation of gustatory with olfactory impulses was largely the occasion for the great development of the primordium hippocampi in fishes. Consistent with this view is the hypothesis that the eversion of the forebrain in ganoids and teleosts was due to the hypertrophy of the olfacto-gustatory correlation center (primordium hippocampi) because of the relatively enormous number and wide distribution of the gustatory organs in these fishes.

Now as compared with the fishes the gustatory apparatus is greatly reduced in amphibians and all land forms. Because of this and because of the mechanical obstacles placed in its pathway by the expansion of the hemisphere and thickening of the corpus striatum, the tractus pallii may have disappeared. In reptiles and mammals ascending gustatory impulses presumably are carried by fibers in the basal bundle which have held their place since fishes and which now run in the stria terminalis as the olfactory projection tract. In the hippocampal formation the correlation of olfactory with general sensory impressions

---

[2] Reference may be made here to the bundles in the human foetus described in the section on the diagonal band. These fibers might be thought of as comparable to the tractus pallii but they probably are connected with the pyriform lobe and not the hippocampus. Also, they join the medial forebrain bundle and go to the hypothalamus within, dorsal to, the optic tract and not outside of the optic tract as in selachians.

(always present) has become more important than the correlation of olfactory with gustatory impressions. Hence the hippocampal formation has not decreased but in reptiles and osmatic mammals has increased in importance.

In amphibians, according to Herrick's description, two tracts are still present, one of which, his dorsal olfactory projection tract, passes above the lateral forebrain bundle to reach the hypothalamus; while the other, his ventral projection tract, passes outside of and below the lateral forebrain bundle, probably to "connect with the adjacent preoptic nucleus and perhaps with the hypothalamus." Certainly the dorsal tract cannot be the homologue of the tractus pallii of fishes. Possibly the ventral tract is the vestige of the tractus pallii which is not entirely lost in amphibians.

I conclude therefore that the amygdala contains the center for correlation of gustatory with olfactory impressions in the opossum and probably in reptiles and mammals. Also, that the gustatory impressions reach the amygdala by way of the ancient tract connecting the lateral olfactory nucleus with the hypothalamus and not by way of the tractus pallii which ran to the primordium hippocampi in fishes and has disappeared in reptiles and mammals. The amygdala is therefore a complex in which olfactory, gustatory and general somatic sense impressions are brought into correlation.

The outgoing impulses from the amygdala of the opossum may be carried by diffuse fibers into the pyriform lobe and the striatum, by the special bundle connecting the basal nuclei with the hippocampus, by the fiber tract of the diagonal band to the hippocampal formation, and by the bundles of the stria terminalis. These bundles lead to the hypothalamus, the preoptic nucleus and the parolfactory area.

c. The amygdala of mammals

Kölliker ('96) has described the general relations of the stria terminalis and the amygdaloid complex in the rabbit. He distinguished four masses which probably correspond to the cortical (*NA*), basal (*N1′*), central (*N1*) and lateral (*N1′*) amygdaloid nuclei, but he called only the first of these the nucleus amygdalæ.

Völsch ('06, '11) has given the fullest account of the morphology of the amygdaloid complex in mammals, based on the study of Erinaceus, Mus, Foetorius, Lemur and Macacus. He describes the following nuclei: 1) nucleus B (and B′ in some forms), most caudal part of the complex, comprising both cortex and deep layers of the lobus pyriformis medial to the sulcus endorhinalis; 2) nucleus T, lateral and rostral to B and deeper, not including cortical layers; 3) nucleus T′, differentiated from T, dorsal internal to T, consisting of large cells; nucleus M, lateral to T and T′, a large nucleus with few myelinated fibers; nucleus D, on the medial surface rostral to B and close up in the sulcus hemisphaericus; nucleus B+D, a rather undifferentiated mass rostral to B, the 'basale Spitzenkern' of earlier authors; nucleus D′, somewhat embedded or enclosed in nucleus D, the nucleus of the lateral olfactory tract of Ganser; nucleus or cell-group E lying between nucleus D and the lentiform nucleus, which may or may not belong to the amygdaloid complex. Völsch saw in the mouse indications that the nucleus T owed its origin to an infolding of the pyriform cortex at the sulcus endorhinalis and suggests the 'speculation' that the whole complex may have arisen in a similar manner. In the carnivore, lemur, and monkey the author groups the nuclei M, T and T′ into what he calls the Hauptkomplex, considers B and D of less importance and in the monkey is unable to find either D′ or the fiber bundle which is connected with it in lower forms.

The stria terminalis enters into the fiber capsule of the Hauptkomplex, the other source for which is the tangential fiber layer of the pyriform lobe. Fibers of the stria also pass through and around this chief complex to reach the intermediate region of the pyriform lobe and nuclei B, D and B—D. A special bundle runs to nucleus D′. This bundle Völsch identifies with the anterior or dorsal limb of the sagittal longitudinal bundle of earlier authors, and says that the caudal or ventral limb runs to the caudal end of the 'Rindenanteil' (*i.e.*, nucleus B and pyriform cortex) which it supplies. The author is not certain that the stria makes any connection with nucleus M. The stria does not enter the nucleus lentiformis.

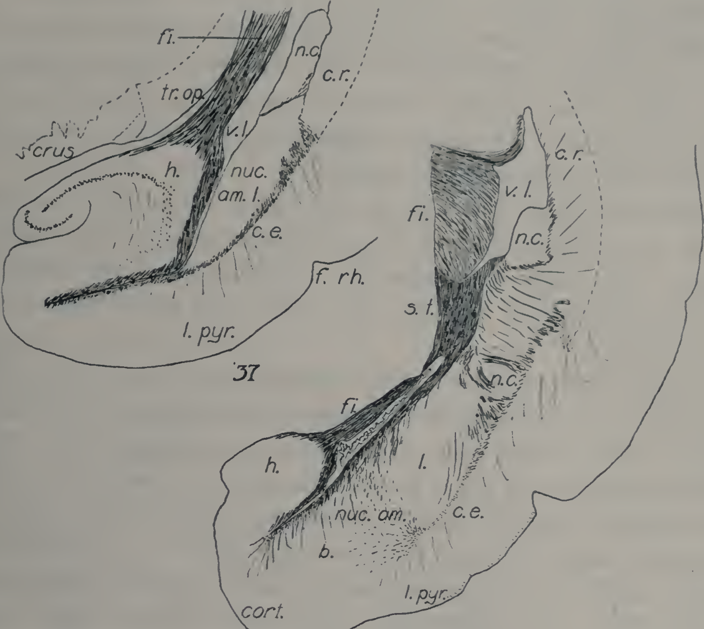
The author recognizes the fusion of the tail of the caudate with the putamen, but assigns too great an extent to the putamen, including part of the amygdala in it, as we shall see below. He does not describe the stria medullaris except to mention a transverse bundle related to nucleus D′ in Erinaceus. In 1906 he is not sure that the tractus olfactorius has any relation to nucleus D′ in Erinaceus, but in his general summary in 1911 he states that it ends in the proximal part (regio olfactiva) of the pyriform lobe, tuberculum olfactorium and in nucleus D′, and enters the capsula externa.

Amygdaloid complex of the rabbit. The general relations will be described first as they appear in a transverse series of sections stained by the Weigert method and then the several nuclei will be examined in cell preparations.

As one follows a transverse series from behind forward the first part of the amygdala to be seen is the great lateral nucleus which appears as a plate of gray matter in the lateral wall of the temporal horn of the ventricle, bounded laterally by the external capsule. There soon appears directly above the lateral nucleus the tail of the caudate as it bends around the internal capsule. The superficial fiber layer of the caudate forms a thin lamina separating it from the lateral nucleus. The external capsule bends round the temporal horn as a ventricular layer of fibers extending to the extreme ventro-medial angle of the ventricle (fig. 37).

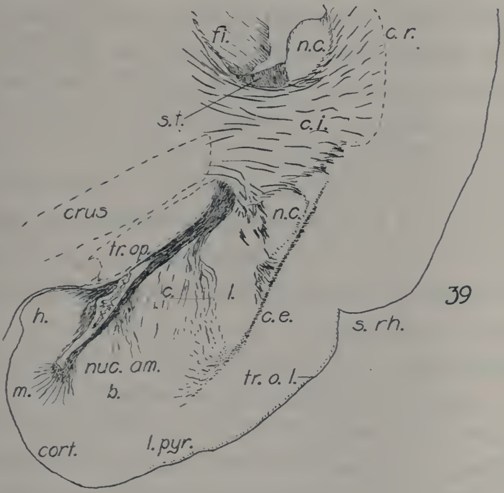
A few sections forward the basal nucleus appears as a thickening of the ventral wall. This nucleus lies outside the ventricular fiber layer while the lateral nucleus lies internal to the external capsule, as in the opossum. Soon the basal and lateral nuclei have thickened so much that they form a nearly vertical side wall to the ventricle. At this level (fig. 38) the external capsule where it meets the lateral border of the basal nucleus divides into two parts as in the opossum: one outside the basal nucleus continuous with the tangential fiber system of the pyriform lobe, and the other internal to the basal nucleus consisting of the numerous

Figs. 37, 38, 39 Sketches from three transverse sections of the rabbit brain in the amygdaloid region. These sections show the position of the amygdaloid nuclei and the distribution of some of the stria terminalis bundles. Note the relations of the lateral and basal nuclei to the external capsule described in the text (p. 422).


fi.
n.c.
c.r.
tr. op.
v. l.
crus
h.
nuc.
am. l.
c. e.
f. rh.
l. pyr.
c. r.
v. l.
fi.
n.c.
s. t.
n.c.
fi.
h.
l.
nuc. am.
c. e.
b.
l. pyr.
cort.

37

38


fi.
n.c.
c. r.
s. t.
c. i.
crus
n.c.
tr. op.
c.
l.
h.
c. e.
s. rh.
nuc. am.
m.
b.
tr. o. l.
cort.
l. pyr.

39

small fascicles penetrating both the basal and lateral nuclei and mingling with fascicles coming from the stria terminalis. The bundles of the stria destined for the basal nucleus are seen coming down from the caudal border of the internal capsule along the outer wall of the ventricle to its extreme tip. The tail of the caudate is pierced by many corona radiata bundles which distinguish it from the lateral nucleus.

Farther forward the lateral nucleus is pierced by a larger number of myelinated fibers from both the stria and the external capsule. Although the essential relations are the same this nucleus in the rabbit is richer in myelinated fibers than it is in the opossum.

The basal nucleus grows much thicker than it is in the opossum and this is one reason for the lateral nucleus being pushed farther caudad. Also, when the central nucleus appears it is placed much farther dorsad than in the opossum. The area of interlaced fascicles from the stria and external capsule holds the same position in the two forms, between the central and basal nuclei medially and the caudate-putamen and the lateral nucleus laterally (fig. 39). The thickening of the ventral wall which pushes the central nucleus dorsad is due in part to the appearance of the medial nucleus adjacent to the extreme medio-ventral tip of the ventricle. With this is connected the stria bundle which runs down along the lateral side of the ventricle (fig. 39). Going on forward the temporal horn of the ventricle disappears and the amygdala grows smaller. It consists of the central, medial, and basal nuclei to which the remaining fibers of the stria are distributed. Finally the commissural bundle descends through the most anterior part of the amygdala to reach the nucleus of the lateral olfactory tract in the ventro-medial tip of the temporal lobe. At the same time appear the bundles of the temporal limb of the anterior commissure.

For the description of the amygdaloid nuclei in the rabbit I shall employ a series of horizontal sections stained with neutral red. In this series the cells are sharply stained to show the chromophile substance and the fiber tracts have a dull brick-red stain sufficient to enable one to identify the chief bundles.

In following such a series from above downward we come to the basal surface of the frontal pole of the brain before reaching the temporal pole, and the amygdaloid complex is most naturally approached from the side of the olfactory tubercle, anterior perforate space and diagonal band. For the relations in this region see the preceding description (p. 375). At this level only the posterior border of the internal capsule is present in the sections. The area in front of this and lateral to the optic tract is occupied by the putamen and globus pallidus as already described. In front of these is the anterior commissure connecting with the thin external capsule. These relations are shown in figure 67 already referred to in connection with the globus pallidus.

The broad area of gray matter in the diagonal band is bounded laterally by the cortex of the anterior perforate space, the medial border of the pyriform lobe and the anterior commissure. The anterior perforate space is separated from the pyriform lobe by the sulcus endorhinalis in which lies the main bundle of the lateral olfactory tract. The cells of the pyriform cortex are closely packed and are much more deeply stained than are those of the anterior perforate space. From the narrow interval between the two in nearly every section cells seem to be wandering in toward the border of the external capsule at the anterior commissure. Lateral to the anterior commissure and internal to the external capsule back to its junction with the corona radiata are found flattened clumps of darkly staining cells (fig. 68). In some sections there is a continuous plate of such cells all the way from the anterior commissure to the caudal border of the corpus striatum. This plate lies along the inner surface of the external capsule while the claustrum parallels this on the outside of the same capsule.

In sections near the caudal and lower border of the internal capsule the following relations are found (fig. 68): The special cortex of the anterior perforate space has just disappeared. The gray mass of the diagonal band fills nearly the whole space between the lobus pyriformis and the preoptic region. At this region it may be said that the diagonal band merges with the amygdaloid complex. The putamen is an elongated oval bounded medially by the posterior border of the internal capsule and the few remaining cells of the globus pallidus. Caudally the nucleus caudatus is fused with the putamen as already described.

Medially between the putamen and the optic tract, there is an elongated triangle of cells whose base meets the diagonal band forward and whose apex imbeds the bundles of the stria terminalis. This is the bed of the stria terminalis already described, whose broader basal and anterior part belongs to the medial and central nuclei. The bed of the stria at this point corresponds to the nucleus of the stria (Begleitkern) noticed by Völsch. Now, far caudally among the bundles of the corona radiata and in the angle between the caudate, the corona and the ventricle appear collections of deeply staining cells continuous with the plates of such cells along the inner surface of the external capsule. All these collections of cells belong to the lateral amygdaloid nucleus, the plate of cells along the external capsule corresponding to the thin anterior portion of the nucleus in the opossum.

Ventral to this level the bundles of the internal capsule enter the corona radiata, the putamen and caudate become broadly fused, the lateral nucleus enlarges into a triangular deeply stained mass behind the caudate-putamen and has a continuous strand of cells extending forward like a mallet-handle to the anterior commissure. The globus pallidus disappears and the putamen likewise except for that portion which is fused with the tail of the caudate. In front of this residuum of the putamen the whole space between the external capsule and the optic tract is occupied by the great central nucleus, the narrow medial nucleus and the thin plate of the lateral nucleus. The central and medial nuclei present no marked differences in character or staining reaction of their cells, except that there are a few more cells of medium large size in the central nucleus. The two nuclei meet in the bed of the stria terminalis. The commissural bundle separated from the rest of the stria is going forward between these two nuclei to the nucleus of the lateral olfactory tract. The area of the diagonal band gradually loses its larger cells and may be regarded as the superficial portion of the medial and central nuclei. The anterior commissure partly joins the external capsule and partly divides into several bundles between which are found the plates and clumps of cells belonging to the anterior border of the lateral deeply staining nucleus. These relations are shown in figure 69.

Within a few sections the putamen-caudate disappears, the lateral nucleus becomes a large triangular mass (fig. 70). The central nucleus continues as a large oval area in the section, having the greater part of the stria terminalis imbedded in its medial border. The medial nucleus occupies the medial wall adjacent to the closing plate of Aeby. The commissural bundle of the stria takes a straight course between the medial and central nuclei to the nucleus of the lateral olfactory tract which now appears as a dense pear-shaped mass of cells at the extreme tip of the temporal pole. Lateral to this appears a broad area of in-wandering cells still related to the lateral nucleus but also giving rise to what will appear in the following sections as the large basal nuclei.

The last section of this series which cuts the nucleus of the lateral olfactory tract (fig. 71) also cuts the ventral border of the central nucleus and shows several dense collections of cells which are really thin irregular plates situated between the central and basal nuclei (intercalated masses). Völsch interprets such clumps or plates as collections of glia. It should be noted, however, that these clumps are located in what Völsch calls the fiber capsule of his 'Hauptkomplex,' between the bundles of the stria and the amygdalo-pyriform network. I think these cells are to be regarded as nerve cells among which these fibers have taken their course during development and that with the growth of the several nuclei of the amygdala, especially the late formation of the basal and lateral nuclei, these cells are caught and held among the layers of fibers and compressed into dense plates and clumps by the expansion of surrounding structures. In a section at this level the lateral nucleus occupies more than half of the area of the whole amygdaloid complex.

In sections immediately below this (fig. 72) there appears in the region of the central nucleus a group of large cells which soon grows into a large and prominent rounded nucleus. Meantime medial to this appears a smaller rounded mass of smaller cells. Between the two is a zone poor in cells, but the two masses form a large ovoid mass lying in front of the lateral nucleus. In front of these is a broad cortical plate extending medially from the medial border of the pyriform lobe. The area of in-wandering cells continues to be clearly visible at the border of the pyriform lobe (sulcus endorhinalis). This broad plate is homologous with the cortical nucleus in Didelphys, while the two masses internal to it correspond to the basal nucleus of Didelphys. Völsch has described these large and small-celled nuclei which he designates T′ and T respectively. He did not find a large-celled nucleus in Erinaceus or Mus. In size, form, and staining properties the large cells present the closest possible resemblance to those of the pyriform cortex. The cells of the small-celled part are paler and closely resemble those of the cortical nucleus. Whether the equivalent of the accessory basal nucleus of the opossum is included in the small-celled nucleus in the rabbit, I am unable to say. It should be noticed that the large-celled nucleus is farther lateral in position in the rabbit than in the opossum. In the absence of any detailed knowledge of differences in their fibers connections I shall speak of the whole mass as the basal nucleus, which consists of large-celled and small-celled portions.

In the following sections approaching the basal surface the lateral nucleus disappears first, then the basal nucleus merges with the cortical layer. Before the basal surface is reached the cortical layer takes on the characters of the pyriform cortex but the sulcus endorhinalis continues to the very end of the series and the appearance of immigration of cells is maintained. The sulcus finally crosses the basal surface of the temporal pole to continue up (dorsad) some distance on the medial surface. Here the appearance of infolding is more marked than anywhere else along the whole sulcus and *the thick bands of in-wandering cells are directly connected with the large-celled basal nucleus* (fig. 73). These facts strongly indicate that the large-celled nucleus was invaginated from the caudal end of the endorhinal sulcus which was carried into the medial wall of the brain by the expansion of the general pallium.

If this is true, it may explain how the large-celled nucleus comes to occupy a lateral position in the mammalian brain while in the turtle the only nucleus of large cells lies next the medial wall. It must be assumed that the thickening of the basal wall to form the cortical and small-celled nuclei took place after the large-celled nucleus had sunk below the surface and these later formations may have pushed the large-celled nucleus lateralward. It is on this basis that the large-celled medial nucleus of the turtle is compared with the basal nucleus in mammals.

Völsch ('06, '11) has distinguished essentially the same nuclei. His nucleus B (and B′) appears to be sub-cortical in Erinaceus and Mus and to include the cortex in higher forms. It corresponds to my cortical nucleus. His nucleus D is my medial nucleus, and his D′ is the nucleus of the lateral olfactory tract. His nucleus T is small-celled in Erinaceus and Mus but has a large-celled part T′ in Foetorius, Lemur and Macacus. His nucleus M is my lateral nucleus, but I cannot accept the merging of nuclei T and M. The two are always sharply separated in the forms which I have studied. Although Völsch has mentioned the appearance of gray in the stria terminalis behind and below the internal capsule and given it the name 'Begleitkern des Stria,' he has failed to appreciate the continuity of this with the medial nucleus or its importance as a bed of the stria terminalis. Völsch also has wholly failed to recognize the central nucleus as one of the chief parts of the amygdaloid complex. He describes a small cell-group E, which he is inclined to think belongs to the amygdaloid complex rather than to the striatum. This cell group undoubtedly is included in my central nucleus, but a large part of the central nucleus is assigned by Völsch to the putamen.

Amygdaloid complex in the bat (*Myotis*). This small North American bat has an amygdala of relatively enormous size. The bed of the stria terminalis above and behind the anterior commissure is very large like that in the rat. Behind this, where both thalamus and corpus striatum are large the gray is reduced to elongated cells among the stria fibers, but is never absent.

Immediately behind the internal capsule the bed of the stria expands into the central nucleus which lies ventral and medial to the putamen-caudate (fig. 77). Lateral to the putamen is the great lateral nucleus. Beneath the central is the medial nucleus, occupying the ventro-medial angle of the hemisphere. Lateral to this is the cortical nucleus and between this and the lateral is the basal nucleus. The latter shows a ventral small-celled part and an internal large-celled part of irregular form. The cortical nucleus is separated from the cortex of the pyriform lobe by an infolding from which cells appear to be migrating into the basal nucleus. Caudal to this level the lateral and basal nuclei are even larger for some distance. The large cells of the basal nucleus are sometimes more medial, sometimes more lateral in position. In nearly every section they show a very intimate relation to the infolding of the pyriform cortex. The sulcus endorhinalis is scarcely visible as an external groove. A section at the caudal border of the lateral nucleus shows the basal nucleus as a simple fold of the ventral wall (fig. 76). The relations here are practically identical with those in the turtle.

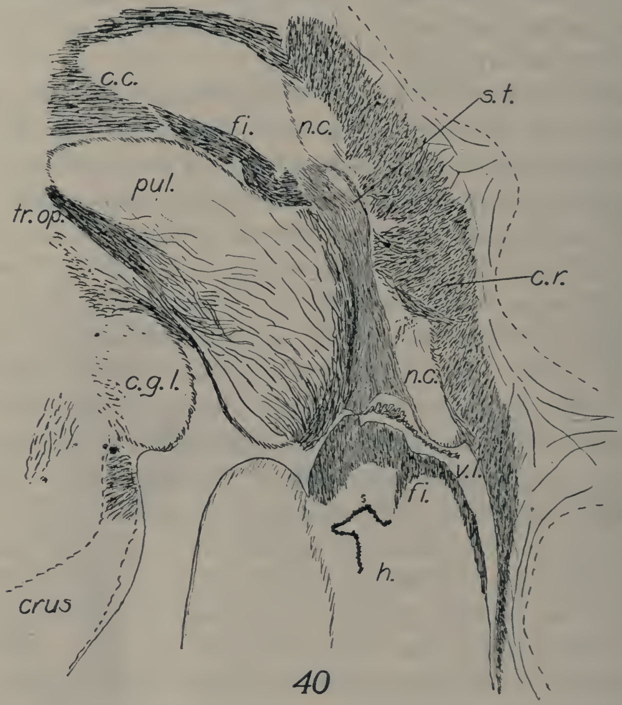
Going forward from the level shown in figure 77 the basal nucleus grows smaller and disappears, the central and medial nuclei merge with the gray of the diagonal band and for a long distance the lateral nucleus rests directly upon the area of immigrating cells. Up to the level of the anterior commissure the region of the cortical nucleus of the amygdala is continued as a small-celled cortical area medial to the sulcus endorhinalis, which is here a well pronounced sulcus. This small-celled area is comparable to the small-celled medial border of the pyriform lobe in the turtle. In both forms this is essentially a part of the lateral olfactory area of lower vertebrates preserved in its primitive form and relations. The appearance of infolding and immigration of the cortical area continues forward beyond the basal and lateral nuclei. At one point (fig. 78), where the diagonal band leads mesad and forward, the small-celled cortical area is itself reduced and infolded so that it appears to bend the gray mass of the diagonal band up against the anterior commissure. This is very interesting in view of the disposition of the diagonal band nucleus in human foetal brains. Forward from this point the small-celled mass regains the surface medial to the sulcus endorhinalis and the immigration of cells ceases. In the next photograph shown (fig. 79, *t.o.*) the small-celled mass blends with the cortex of the tuberculum olfactorium. The small-celled band continues on forward to join with the medial olfactory area in front of the tuberculum.

The bat shows better than any other form studied the primitive relations of the pyriform lobe and amygdala and the direct relation of the basal and lateral nuclei to the process of immigration of cells from the line of the sulcus endorhinalis. It is especially noteworthy that the lateral nucleus is massive at its anterior end where it retains its connection with the involution area, while this portion is thin in the opossum and rabbit.

Although the fibers are not stained in these sections, it will be of interest to add a word on the disposition of the anterior commissure. The greater part (or at least the most compact bundle) of its fibers reaches the pallium by bending up over the internal surface of the lateral amygdaloid nucleus. The remainder spreads somewhat in several bundles which go beneath the lateral nucleus to reach the external capsule or enter the amygdala. For some distance the lateral nucleus thus appears to be surrounded by a triangle of fibers composed of the limbs of the anterior commissure and the external capsule. Still other bundles of the commissure spread out around the anterior end of the lateral nucleus to reach the external capsule in essentially the same way as in other mammals. The internal capsule is widely dispersed in many small bundles through the putamen.

The amygdaloid complex in the monkey. I have for this study a series of transverse sections of the brain of Macacus rhesus stained by the Weigert method.

The tail of the caudate in Macacus is a very slender mass of gray matter covered by a thin layer of fibers. In transverse sections cutting the caudal border of the internal capsule the caudate and the stria terminalis lying side by side are of almost equal size. It is obvious in Weigert sections that the stria contains gray matter independent of the caudate. The ventricular fibers of the stria are deeply stained, the middle layers next the caudate are paler and more diffuse, and the deep fibers next the internal capsule are coarser and more deeply stained. The caudate enlarges slowly forward from this point and more rapidly backward, as it descends into the temporal pole. The caudate is traversed by bundles of the internal capsule and small fascicles seem to end in it. Several small islands of gray matter related to the caudate are seen along the corona radiata. Toward the temporal pole the caudate continues to enlarge and these islands imbedded in the corona radiata greatly increase in size. Soon it



Figs. 40 to 43 Sketches from a series of transverse sections of the brain of the monkey, Macacus rhesus, stained by the Weigert method. Figure 40 is the most caudal.

Fig. 40 This section shows the stria as it curves about the caudal surface of the internal capsule and cuts the caudate nucleus twice, above and below the internal capsule. The caudate is very slender at this point in the monkey.

is seen that these represent the upper border of the putamen which is imperfectly separated from the caudate by the posterior bundles of the internal capsule.

The stria as it descends toward the temporal pole becomes flattened against the superficial fiber layer of the external geniculate body and its deepest bundle is wedged into the narrow angle between this and the internal capsule. On the face of the external geniculate body is a thin layer of fibers which take a deeper stain than the rest of the stria. This will prove to be the bundle of stria medullaris fibers coming up from the nucleus of the lateral olfactory tract. In sections which pass through the lower border of the external geniculate body the gray bed of the stria begins to increase in volume and the component bundles of the stria are separated.

A few sections farther forward (fig. 41) the bed of the stria expands into a distinct central nucleus, and below it are the medial, basal, and lateral nuclei side by side. The stria passes through the central nucleus and fans out to the three nuclei below. The bundle to the lateral nucleus does not show connection with the stria in this section because just here it bends forward around the ventricle. The central nucleus lies between the optic tract and the putamen. Its upper border is in contact with the lower angle of the globus pallidus.

From this point forward two longitudinal bundles are seen running through the substance of the amygdala. The first lies between the medial and basal nuclei. In addition to fibers for those nuclei it seems to contain the commissural bundle for the nucleus of the lateral olfactory tract.

The second lies between the central nucleus above and the lateral part of the basal and the lateral nucleus below. It corresponds to the sagittal longitudinal bundle in the rabbit. A little farther forward a broad bundle comes down from the stem of the stria through the central nucleus to join this bundle. Many of these fibers run directly down past the longitudinal bundle to spread out between the basal and lateral nuclei (figs. 41, 42, 43). All the while the tangential fiber layer of the pyriform lobe and its connection with the corona radiata hold essentially the same relation to the external surface of the basal and lateral nuclei as they do in the rabbit. The broad sheets of small fasciculi spreading through the basal and lateral nuclei run actually to meet this arm of the corona radiata and it must be assumed that they contain fibers which pass between the pyriform lobe and the amygdaloid nuclei or the stria terminalis or both. Such fibers may thus enter the longitudinal bundle, which would then be appropriately described as an amygdalo-pyriform correlating bundle as in the opossum and rabbit.

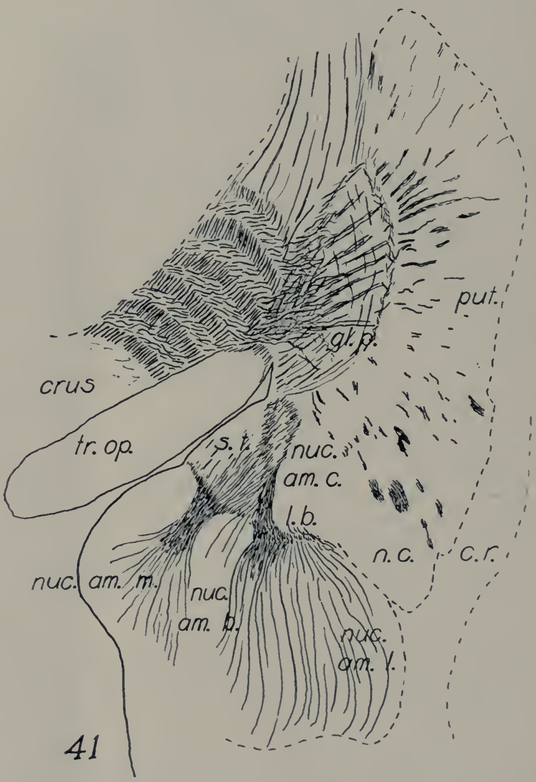


Fig. 41 The bed of the stria has expanded into the large central and medial nuclei and a large bundle of fine fibers corresponding to bundle *2* of the opossum is being distributed to these nuclei. The bundle of coarse fibers to the basal and lateral nuclei is perhaps comparable to bundle *4* of the opossum.

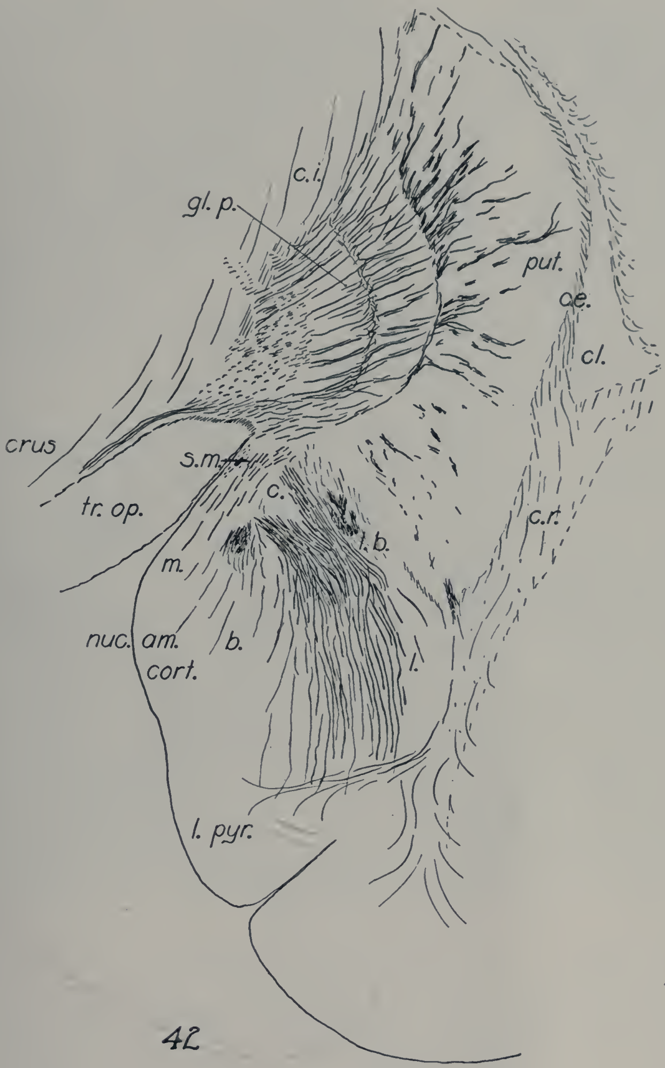


Fig. 42 A broad sheet of fibers passing down through the basal and lateral nuclei brings the stria system into relation with the pyriform cortex. The longitudinal bundle runs in the upper part of this. The olfactory projection tract (bundle *2* of the opossum) is intimately related to both. The compact bundle near the medial nucleus is probably the commissural bundle of the nucleus of the lateral olfactory tract. The small stria medullaris bundle is described in the text (p. 442).

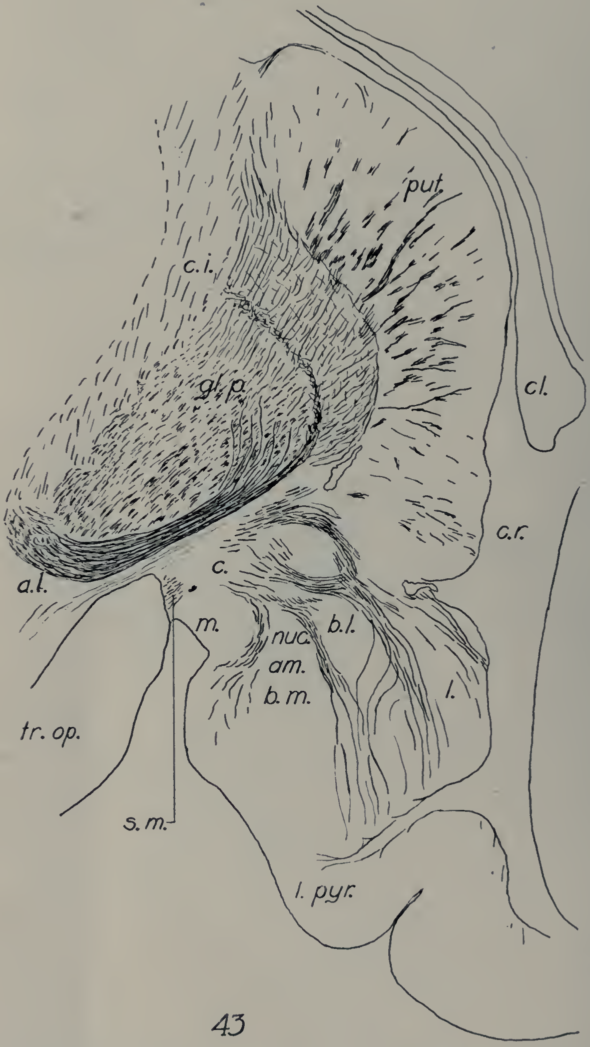
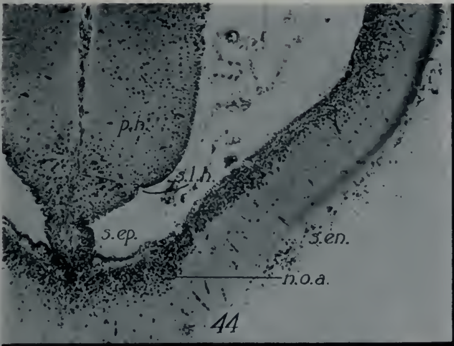
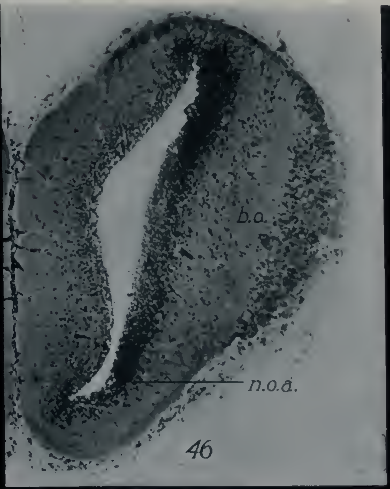
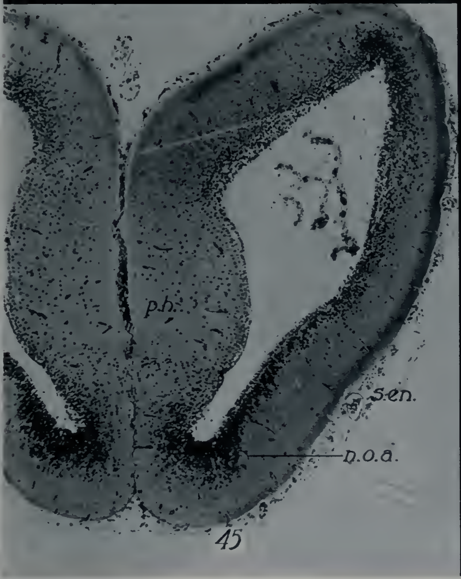
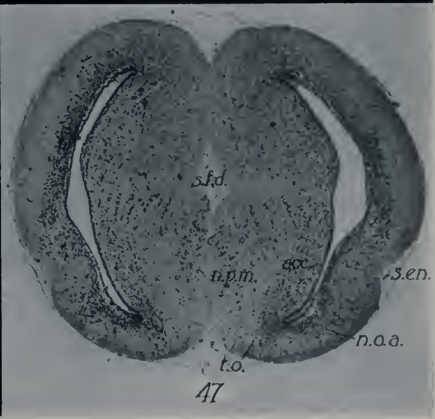


Fig. 43 Through the rostral part of the amygdala. The outgoing fibers from the longitudinal bundle and the pyriform cortex form two bundles resembling in section the sign ( ). The basal nucleus is divided into medial and lateral parts by a lamina of stria fibers.









Figs. 44, 45, 46 Three transverse sections through the rostral part of the telencephalon of Cryptobranchus between the septum ependymale and the olfactory bulb. The nucleus olfactorius anterior forms a dense collection of cells about the ventral angle of the ventricle. A part of these cells together with the few cortical cells represent the tuberculum olfactorium. The slight ridge bulging into the ventricle opposite *s.en.* corresponds to the bed of the stria terminalis in reptiles and mammals.

Fig. 47 A transverse section of the brain of the frog through the caudal part of the nucleus olfactorius anterior. × 21. Here the common mass of the stria bed and nucleus accumbens is deeply incised by the ventral angle of the ventricle. Farther forward the nucleus olfactorius anterior is a thick rounded nucleus less deeply indented by the ventricle.

The stria medullaris bundle mentioned above can be traced down along the external face of the optic tract. Before it reaches the nucleus of the lateral olfactory tract a small dense bundle on the right side and several such bundles on the left side become detached from it (figs. 42, 43). Their destination will be mentioned later. A short distance farther forward the main bundle of the stria medullaris detaches itself from the optic tract and spreads as diffuse fibers in the direction of the medial nucleus. The fibers of the first longitudinal bundle end at the same level. Although there is no distinct collection of cells visible in Weigert preparations, I believe that a small nucleus of the lateral olfactory tract is located here at the anterior border of the medial nucleus, which is the location of that nucleus in other forms. The lateral olfactory tract is seen in sections a little in front of this level.

Through the anterior half of the amygdala the basal nucleus appears to be divided by a vertical lamina of stria fibers (fig. 43). The medial part is doubtless small-celled, the large-celled part being turned over to the lateral position through the rotation of the temporal pole resulting from the expansion of the general pallium. We shall see the same relationship in human foetal brains.

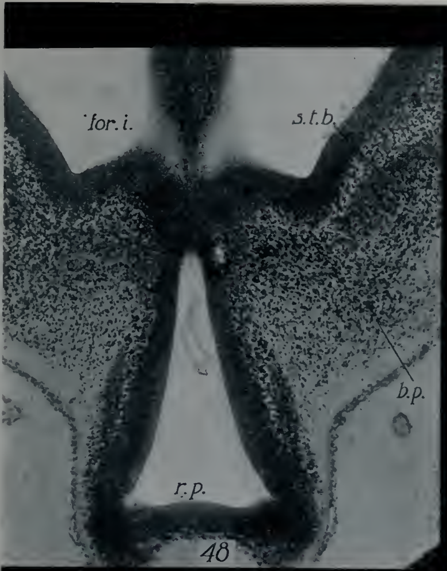
Figs. 48, 49, 50, 51 Four transverse sections of the telencephalon of an embryo of Chelydra serpentina of 8½ mm. carapace. × 62.

Fig. 48 Through the anterior wall of the interventricular foramina and slightly behind the anterior commissure. The commissure bundles approaching the median plane from either side are imbedded in masses of cells which are in close relation with the stria bed.

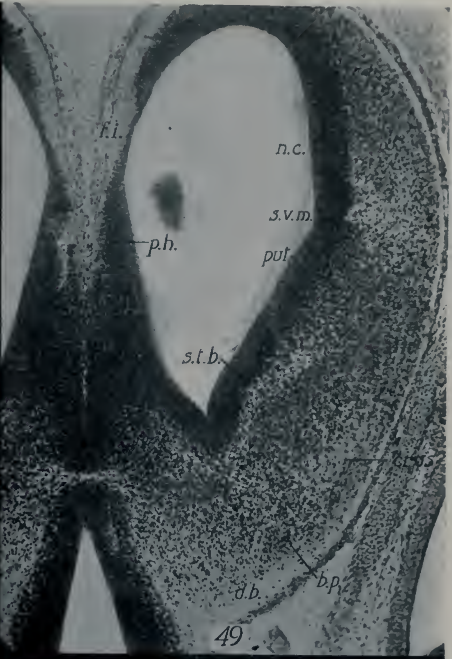
Fig. 49 Through the anterior commissure. The bed of the commissure here shows a close relation also with the basal proliferation which gives rise to the tuberculum, anterior perforate space, etc. The letters *put.* indicate the proliferation of cells going to join the putamen which is already well formed in the lateral wall. The proliferation for the nucleus caudatus is well under way and the wall begins to bulge slightly into the ventricle (dorsal ventricular ridge).

Fig. 50 Section just in front of the preoptic recess, and just behind the tuberculum olfactorium. The ventral angle of the ventricle is beginning to descend into the ventricle of the tuberculum (fig. 51). In this and figure 51 may be seen the close relation of the stria bed, the nucleus accumbens and the basal proliferation which is beginning to form the tuberculum. Farther forward these structures become more closely united in the nucleus olfactorius anterior.

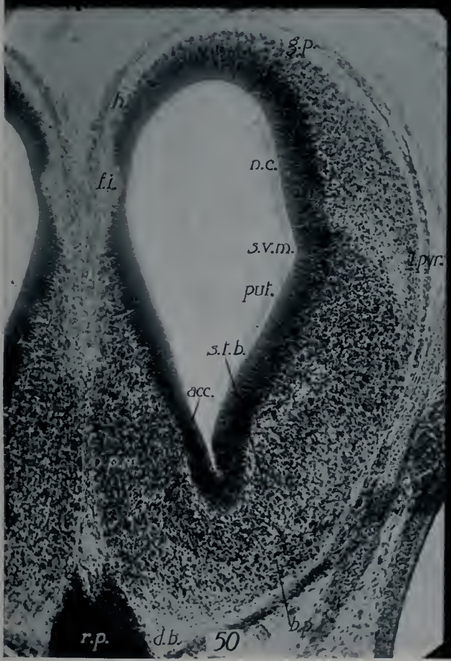
Fig. 51 Through the tuberculum olfactorium. The precommissural fiber system is seen on the medio-ventral surface.


for. i.
s.t.b.
b.p.
r.p.

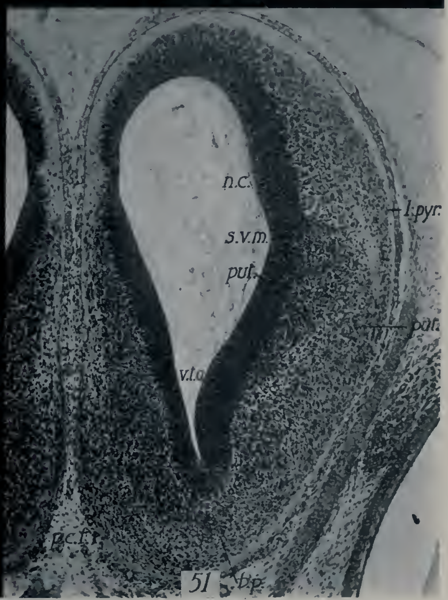
48


f.i.
n.c.
s.v.m.
p.h.
put.
s.t.b.
c.os.
b.p.
d.b.

49


g.p.
h.
f.i.
n.c.
s.v.m.
l.pyr.
put.
s.t.b.
acc.
r.p.
d.b.
b.p.

50


n.c.
l.pyr.
s.v.m.
put.
put.
v.t.o.
p.c.f.
b.p.

51

Opposite the amygdala the external capsule is greatly thickened and is indistinguishably bound up with the corona radiata of the temporal lobe. Toward the anterior end of the amygdala the larger part of the fibers of the corona radiata collect into the anterior commissure and the external capsule, now a thin band, is separated from the corona radiata by the claustrum. As the anterior commissure collects, many bundles and small fascicles run through the lateral amygdaloid nucleus.

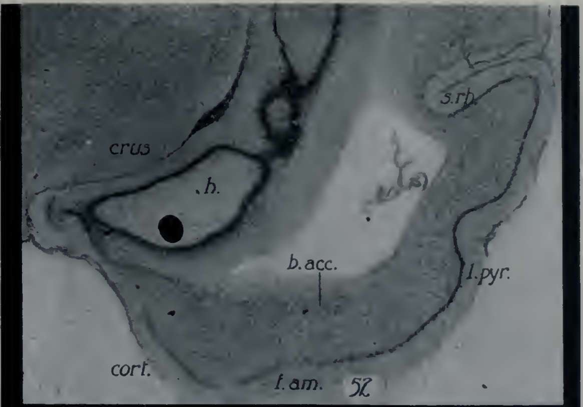
Meantime important changes are taking place in connection with the amygdalo-pyriform association bundle (sagittales Längsbundel). Mention was made of fibers from the stria passing down beneath this bundle to be distributed to the basal and lateral nuclei. Fibers continue in this position so far forward that they can scarcely all be ascribed to the stria. They seem rather to enter a system of fibers directed forward and mesad beneath the globus pallidus. At the same time another rather diffuse bundle rises from the amygdalo-pyriform association bundle, runs in the dividing zone between the central nucleus and the putamen, and joins the same fiber system. These two bundles are shown in figure 43 where they appear like the two elements of a sign of parenthesis ( ). These fibers run on mesad beneath the globus pallidus and join the general system of precommissural fibers passing up through the parolfactory area. They may be regarded as one of the deep components of the diagonal band fiber system.

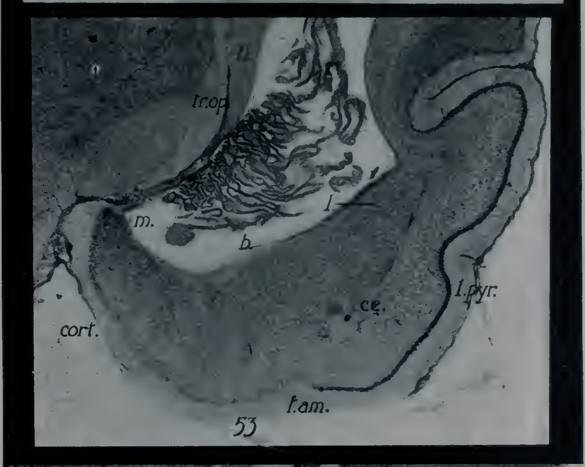
Figs. 52 to 61 Transverse sections of the brain of the opossum, Didelphys virginiana from the temporal pole to the olfactory peduncle to show the structure and relations of the corpus striatum, amygdaloid complex, etc. Neutral red. × 10. Sections are 45 μ thick.

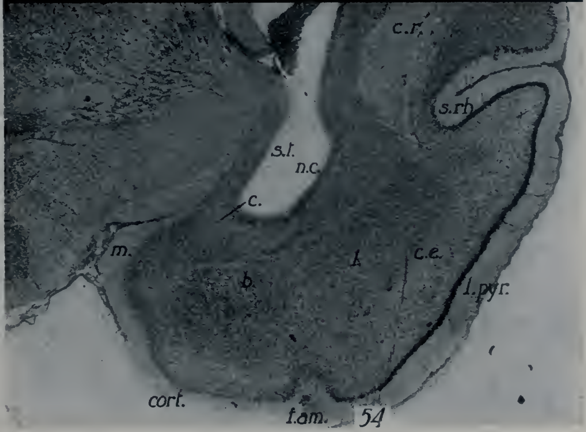
Fig. 52 In the caudal part of the temporal pole, showing the accessory basal nucleus as a collection of irregular clumps of cells. The area medial to the amygdaloid fissure (*cort.*) is continuous with the pyriform cortex, but because of its history in mammals it is assigned to the amygdaloid complex.

Fig. 53 Section 1 mm. forward from the last. The medial, basal and lateral nuclei have appeared. Compare with figures 29 to 31 for the position of the lateral and basal nuclei with reference to the external capsule.

Fig. 54 Section 0.6 mm. forward from the last. The lateral and basal nuclei are larger. The central nucleus has appeared and the stria bed descends over the internal capsule to expand into the central and medial nuclei. The immigration of cells at the amygdaloid fissure is evident. The large-celled (dorsal) and small-celled (ventral) portions of the basal nucleus can be distinguished.


crus
h.
s.rh.
b.acc.
l.pyr.
cort.
f.am.
52


n.
tr.op.
l
m.
b.
ce.
l.pyr.
cort.
f.am.
53


c.r.
s.rh.
s.t.
n.c.
c.
m.
b.
l
c.e.
l.pyr.
cort.
f.am.
54

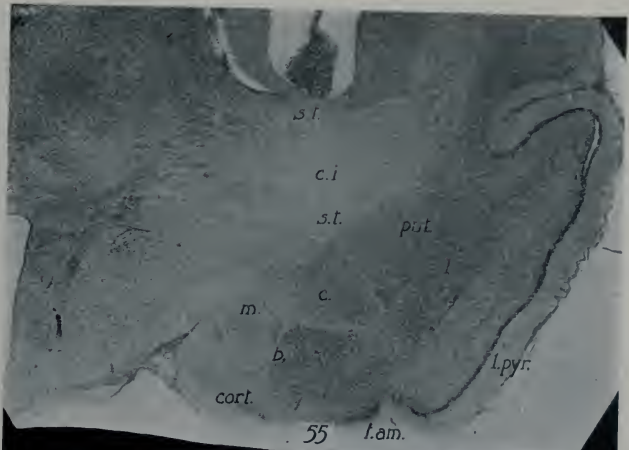
After these special bundles are given off the general diffuse fiber network related to the basal and lateral nuclei (and to the amygdalo-pyriform system above described) collects into a fiber mass lying ventral and internal to the anterior commissure. This fiber mass then turns mesad and, following along beneath the anterior commissure, joins the precommissural system also. Thus a part of the fibers of the amygdalo-pyriform association bundle together with many fibers coming out of the basal and lateral nuclei directly go to form a diffuse but large and important tract which is incorporated in the precommissural fiber system and may in part go to the septum pellucidum and through the fimbria to the hippocampus. It has long been known that fibers of the diagonal band proper, lying on the basal surface of the brain, take such a course, but the existence of such fibers so deep in the brain immediately beneath the anterior commissure has not before been recognized, so far as the writer is aware. This deep system very greatly increases the total volume of fibers going out from the amygdaloid complex and it is worthy of emphasis that these fibers run in distinctly olfactory pathways.

The small bundles mentioned above which detach themselves from the stria medullaris before that bundle enters the nucleus of the lateral olfactory tract, can be traced as very distinct fascicles forward into the diagonal band system just described, but as the other fibers pass on into the precommissural system these small bundles lag behind and come to lie in the sulcus between the lateral olfactory tract and the tuberculum olfactorium. Here

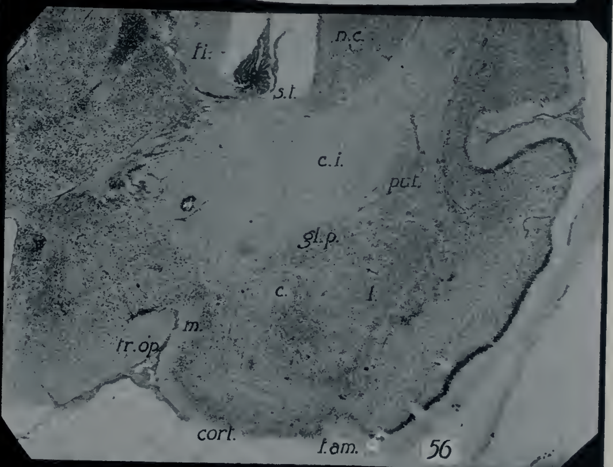
Fig. 55 Section 0.7 mm. forward from the last. Continuity of stria bed and the central and medial nuclei. Strands of cells leading from the amygdaloid fissure to the lateral nucleus.

Fig. 56 Section 0.6 mm. forward from the last. The basal nucleus has disappeared while the lateral is thin and is partly broken up into masses of cells. The central nucleus is still large.

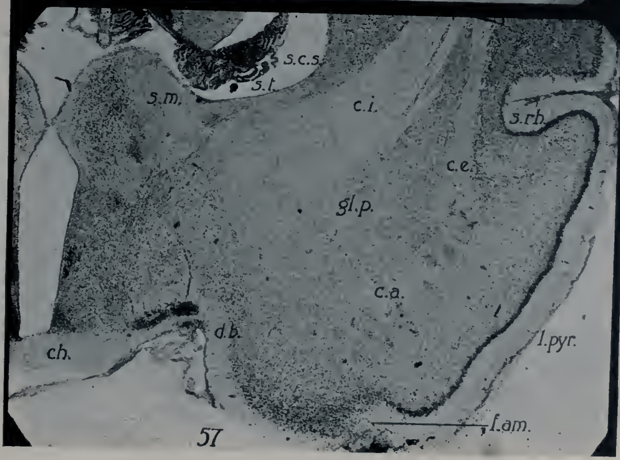
Fig. 57 At the level of the optic chiasma. The oblique strands of cells running from *s.t.* toward *ch.* represent the postcommissural portion of the stria bed in which the olfactory projection tract descends. The strands of cells are packed between the fibers of that tract. Compare figure 35 which is a little farther forward than this. Note the cells among the stria bundles in the floor of the ventricle. Among the anterior commissure bundles are small masses of cells belonging to the lateral amygdaloid nucleus.


s.t.
c.i
s.t.
put.
l
c.
m.
b,
l.pyr.
cort.
f.am.

55


fi.
n.c.
s.t.
c.i.
put.
gl.p.
c.
l.
m.
tr.op.
cort.
f.am.

56


s.c.s.
s.t.
s.m.
c.i.
s.rh.
c.e.
gl.p.
c.a.
l
l.pyr.
d.b.
ch.
f.am.

57

can be recognized the vestige of the ancient lateral olfactory nucleus. The fibers in question may arise from cells of this nucleus or from the adjacent tuberculum. These are perhaps comparable with the fibers in the opossum which come from the tuberculum (p. 395).

The lateral amygdaloid nucleus has an unusual forward extent in the monkey. It continues on beneath the anterior commissure nearly to the level of the caudal border of the tuberculum olfactorium. Here it comes into contact probably with deep gray related to the diagonal band as previously described (p. 374).

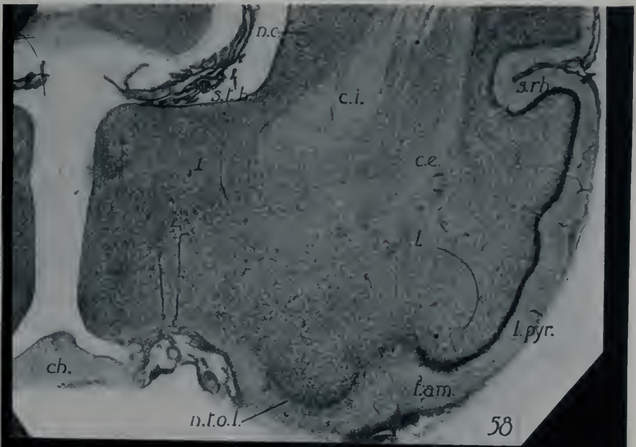
The amygdala in human foetal brains. It will be best to give first a description of the amygdala as it appears in the brain of foetus of 175 mm. and to follow this with an examination of younger and older specimens.

Foetus H. 27, 175 mm. C. R. Beginning with the sections which cut the caudal border of the internal capsule we find the thick mass of undifferentiated ventricular cells corresponding to the caudate occupying a great semilunar area continuous with the ventricular layer of the pallium. Adjacent to the sulcus hemisphaericus the stria terminalis bends down over the internal

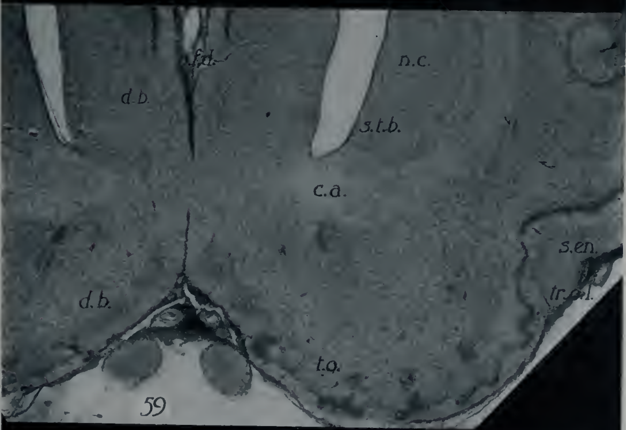
Fig. 58 Eleven sections forward from the last. Between the nucleus of the lateral olfactory tract and the pyriform cortex the fissura amygdalæ shows clearly the immigration of cells in the direction of the lateral amygdaloid nucleus. The stria bed is large here behind the anterior commissure. The arrangement of cells on the medial face of the internal capsule is due to bundle *2* of the stria. Compare figure 35. The commissural bundle (*1*) is seen cut across.

Fig. 59 Through the rostral border of the anterior commissure. The upper end of the diagonal band nucleus is seen just below the fimbrio-dentate sulcus. Below the commissure the nucleus bends around the medio-ventral angle of the hemisphere. The section passes through the caudal part of the tuberculum in which islands of Calleja are seen. The continuation of the fissura amygdalæ here bounds the tuberculum laterally and goes by the name of sulcus endorhinalis because there is no immigration at this level. The sulcus is occupied by the lateral olfactory tract.

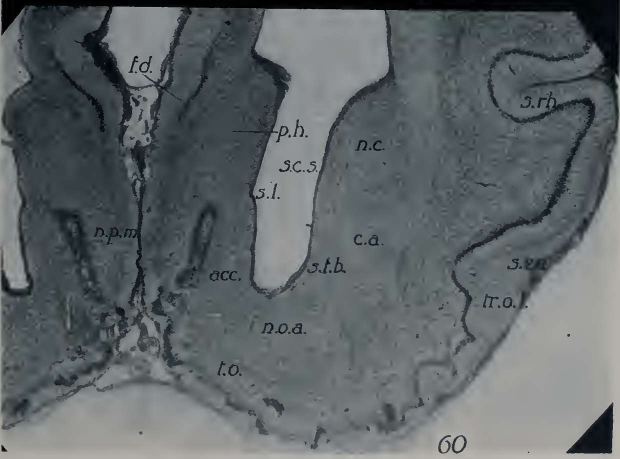
Fig. 60 Through the middle of the tuberculum olfactorium. In the medial wall the nucleus of the diagonal band is replaced by the medial parolfactory nucleus which is closely related to the primordium hippocampi above and laterally. The primordium is bounded below by the ventricular sulcus limitans hippocampi. A thick mass of tuberculum cells rises to this level like the rim of a bowl. The concavity of the bowl (*t.o.*) is filled by the anterior olfactory nucleus, nucleus accumbens and bed of the stria terminalis. The stria bed is seen on the medial surface of the anterior commissure and is bounded above by a slight strio-caudate sulcus.


n.c.
s.t.b.
c.i.
s.rh.
c.e.
l.
l.pyr.
ch.
t.am.
n.t.o.l.

58


f.d.
n.c.
d.b.
s.t.b.
c.a.
s.en.
tr.o.l.
d.b.
t.o.

59

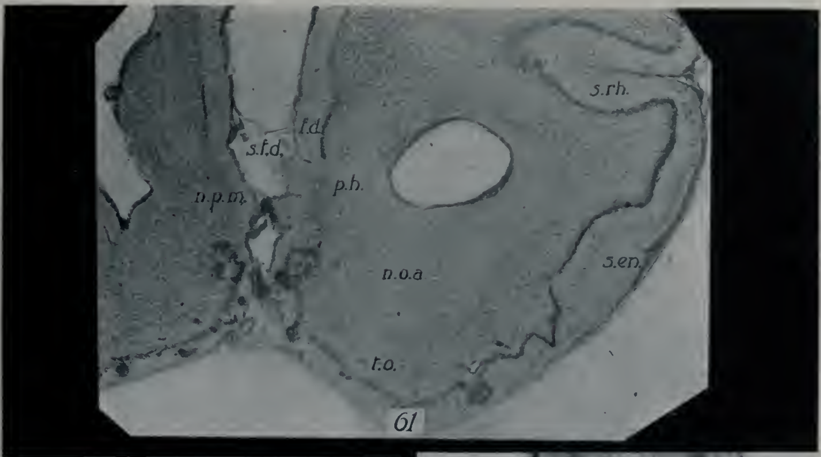

f.d.
s.rh.
p.h.
n.c.
s.c.s.
s.l.
n.p.m.
c.a.
acc.
s.t.b.
s.en.
tr.o.l.
n.o.a.
t.o.

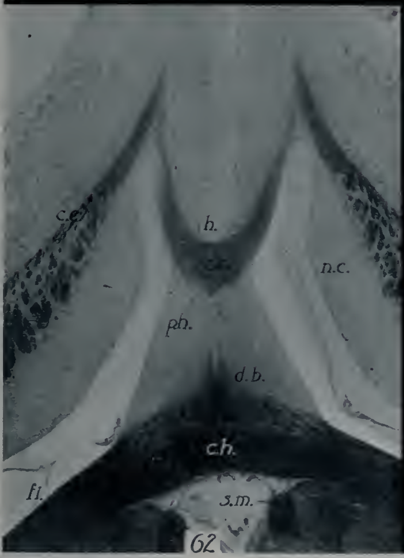
60

capsule and has imbedded in it small masses of cells. The part of the ventricular layer related to the stria, which is large anteriorly, is very small here.

In a few sections the stria descends across the anterior wall (floor) of the temporal horn of the ventricle, where it forms a distinct ridge. The fibers here pass through the extreme caudal border of the basal nucleus and spread like a fan to enter the cortical nucleus. In the same section the lateral nucleus appears lateral to the ventricle. Three sections farther forward (fig. 83) two large bundles are seen entering the basal and cortical nuclei while other bundles destined for the central, medial and lateral nuclei are noted above the ventricle in the elongated bed of the stria. The medial nucleus is just appearing in the medial wall and in the next section shown (fig. 84) both medial and central nuclei are present and a large part of the stria is imbedded in the latter. Now the basal nucleus is clearly subdivided by a lamina of stria fibers, giving the appearance of twin nuclei. The area of cell-immigration lies directly below this dividing line (*f.am.*) and there is a clear indication of infolding of the cortical layer. The lateral nucleus is large, triangular in section and shows distinct lobulation on its outer surface due to fascicles of the corona radiata and of the anterior commissure running along the external capsule pressing into it. This condition is much more pronounced in older foetuses (see fig. 102). The putamen (and globus pallidus) is the small triangular area between the internal capsule and the rounded mass of darkly stained ventricular cells.

From this level forward the basal and lateral nuclei maintain for some distance the size and relations shown in figure 84, while the medial and central nuclei grow larger. The posterior limb of the internal capsule disappearing, the portion of the putamen adjoining the amygdala joins the dorsal larger portion. The central nucleus now consists of a compact rounded mass and of an area of diffuse cells reaching up to the border of the globus pallidus (fig. 85). The basal nucleus is decreasing in area and the lateral part of the lateral nucleus is divided into many small dense masses of cells by the bundles of the corona radiata. In the upper part of the basal nucleus and between the lateral





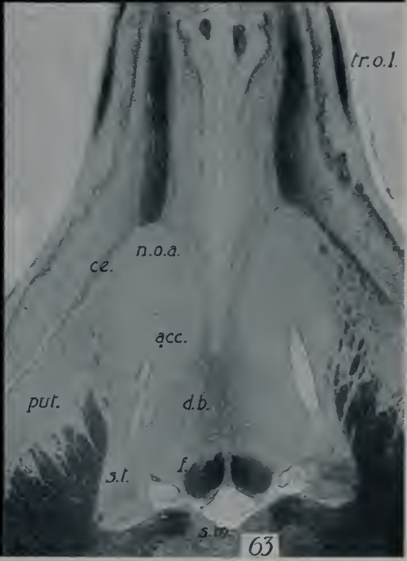


Fig. 61 Through the rostral part of the tuberculum and the anterior olfactory nucleus.

Figs. 62 to 67 Horizontal sections of the brain of a rabbit stained with neutral red. × 6.7. These sections show the relations of the diagonal band nucleus, the stria terminalis, caudate nucleus and all parts of the amygdaloid complex. They are fully described in the text. Owing to some peculiar quality of the stain the photographs have made the fibers much more prominent than they appear to the eye.

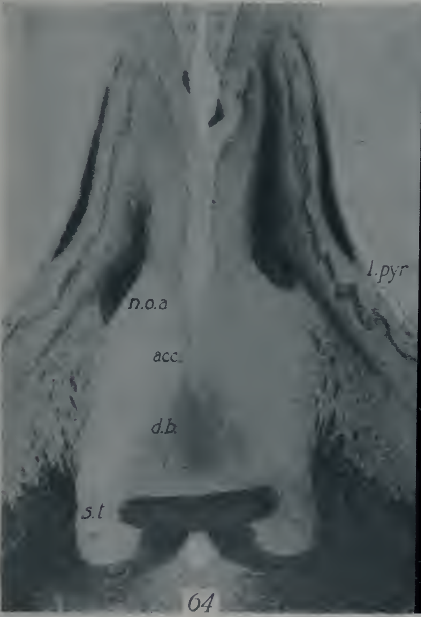
Fig. 62 A section through the septum pellucidum where the fornix columns join the hippocampal commissure. The photograph shows the extreme dorsal end of the nucleus of the diagonal band (*d.b.*).

Fig. 63 Above the anterior commissure. This shows especially well the general relations of the stria bed, the anterior olfactory nucleus and the nucleus accumbens. The very lightly stained bundle along the medial surface of *n.o.a.* and *acc.* is the fasciculus marginalis.

nucleus and the putamen is a network of fibers part of which is condensed into a definite 'sagittal longitudinal bundle.' Parts of this network extend dorsad around either side of the rounded mass in the central nucleus, producing an appearance somewhat like the sign of parenthesis, just as in Macacus. Now from these amygdaloid fibers there is formed in the dorsal part of the central nucleus a distinct bundle which continues forward beneath the anterior commissure, turns mesad and is traced eventually to the tuberculum olfactorium (figs. 85 to 88, *z*). This specific bundle is small and probably contains only a minor part of the fibers which enter or leave the amygdala by this route. It lies in the midst of a rather broad area of diffuse fibers which enters the deep part of the diagonal band system. The more superficial part of this system, in the lower forms studied, is related to at least the central and medial nuclei of the amygdala. Attention is drawn here to the fact that fibers lying deep in the brain, close to the anterior commissure, and connected with the sagittal longitudinal bundle of the amygdala belong to the diagonal band system. This constitutes one of the chief pathways of connection for the lately formed basal and especially lateral nuclei. The fiber tracts connected with the lateral nucleus enter that nucleus by its anterior end. This is what we should expect since we have found it formed in the rabbit and bat by immigration of cells in this anterior region. Evidence of a similar mode of formation in man will be mentioned below.

Forward from the level of figure 85 the basal and medial nuclei rapidly disappear from the sections. The place of the medial nucleus is taken by a rounded medial prominence which probably indicates the position of the nucleus of the lateral olfactory tract (fig. 86). Neither of the fiber bundles related to that nucleus are seen in this brain. The lateral nucleus becomes thin and is more and more broken up by bundles of the anterior commissure passing across it. The central nucleus continues as a large area which merges with the diagonal band.

In this foetus appear certain bundles closely associated with the anterior commissure which descend into the temporal pole mingled with the distributing bundles of the commissure. They are shown in figures 86 and 87. They cross the preoptic region as if to run up in the precommissural fiber system. They may be a part of the diagonal band fibers which go beyond the amygdaloid complex to be distributed to the pyriform lobe. Or, they may turn into the lateral amygdaloid nucleus. These bundles will be referred to as the system *y*.



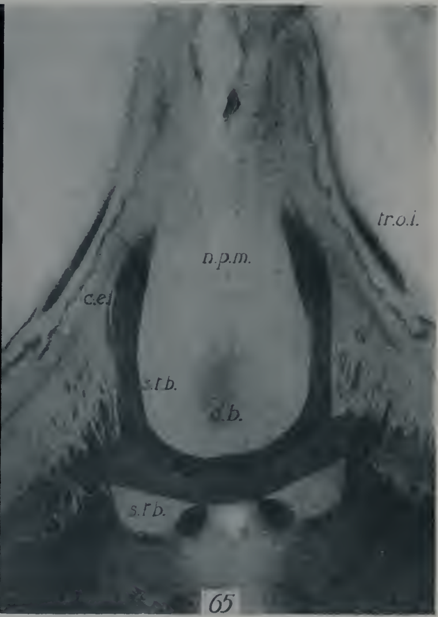


Fig. 64 Through the dorsal border of the anterior commissure. Only the commissural bundle of the stria terminalis is clearly visible. Note that in this figure and the next the stria bed extends forward medial to the anterior limb of the anterior commissure. The true caudate nucleus is largely filled with internal capsule bundles as in the rat.

Fig. 65 Through the anterior commissure. Note that the stria bed continues down behind the commissure lateral to the fornix columns. This is the bed of the hypothalamic bundle or olfactory projection tract.

The amygdaloid nuclei of this foetus correspond closely to those of the opossum, rabbit, bat and monkey, namely, a central, medial, a basal which is subdivided, a cortical and a lateral, and these have so far as can be observed in material stained as this is, the same relations to the chief fiber tracts. The differentiation of cells has not gone on far enough to show which nuclei are destined to possess large cells.

Foetus H. 2, 145 mm. C.R. In this foetus the nuclei of the amygdaloid complex are nearly as well formed as in H. 27 and the general relations agree in every way. I give only one photograph (fig. 81) showing the general relations of the nuclei and the bundles of the anterior commissure and corona radiata descending through the lateral nucleus.

In this brain a bundle emerges from the right amygdala among the bundles of the anterior commissure, separates from the commissure and runs to the tuberculum olfactorium. Here after traversing the tuberculum it either becomes intimately mingled with a bundle of the stria marginalis in the tuberculum or itself joins the stria marginalis to go up in the pre-commissural fiber system.

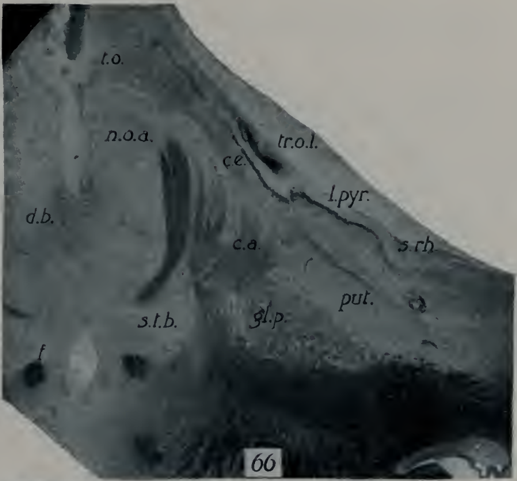
Foetus H. 26, about eight months. This brain was cut in a coronal series and stained with neutral red. The photographs, owing to the low powers used in order to show general relations, do not do justice to the brilliant stain. This brain is cut in nearly the same plane as the rabbit brain and the amygdaloid complex is best approached from the side of the diagonal band.

In a previous section (p. 378) the spreading of the gray matter of the diagonal band in the area medial to the external capsule and rostral and ventral to the globus pallidus has been described. In sections basal to that shown in figure 97 the central and medial

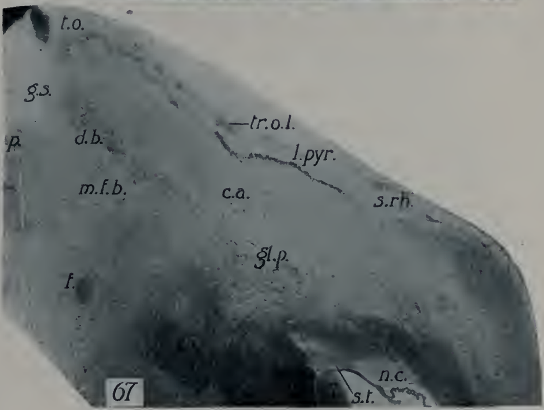
Fig. 66 Just beneath the anterior commissure. The spreading of the posterior limb of the commissure piercing the front part of the internal capsule is well seen on the right. The tuberculum olfactorium now appears. Its relation to medial and lateral olfactory areas is evident. The lateral olfactory tract occupies the sulcus endorhinalis.

Fig. 67 Near the basal surface of the frontal lobe. The nucleus of the diagonal band spreads backward. The large cells of the globus pallidus are well seen.

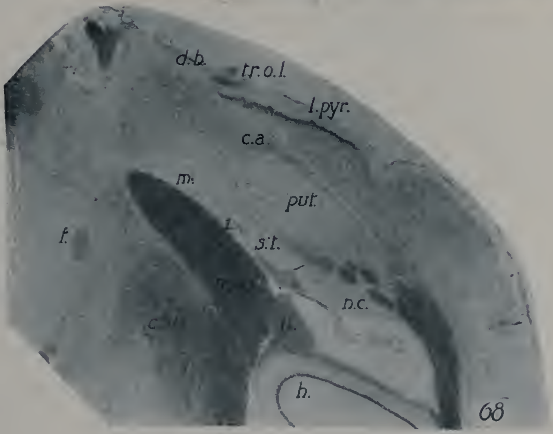
Fig. 68 The nucleus of the diagonal band with its large cells is still present. The nucleus caudatus and putamen are imperfectly separated by the posterior bundles of the internal capsule. The stria terminalis runs downward and forward parallel with the optic tract and the stria bed expands into the medial nucleus. The commissural bundle destined to the nucleus of the lateral olfactory tract has separated from the remainder of the stria. Along the external capsule caudal to *c.a.* are cords and plates of cells which belong to the lateral nucleus.


t.o.
n.o.a.
tr.o.l.
c.e.
l.pyr.
d.b.
c.a.
s.rh.
put.
s.t.b.
gl.p.
f.

66


t.o.
g.s.
tr.o.l.
p.
d.b.
l.pyr.
m.f.b.
c.a.
s.rh.
gl.p.
f.
n.c.
s.t.

67


d.b.
tr.o.l.
l.pyr.
c.a.
m.
put.
f.
s.t.
n.c.
h.

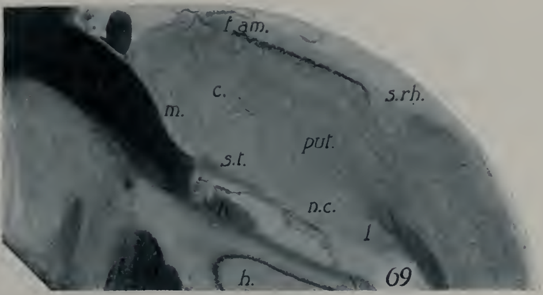
68

nuclei of the amygdala appear in close relation to the diagonal band (fig. 98). The central nucleus is bounded laterally by the anterior commissure bundle, the lower part of the putamen and the internal capsule. The stria terminalis is imbedded in the medial border of the central nucleus and one bundle penetrates the medial nucleus. The medial nucleus meets the hippocampal formation at the closing plate of Aeby.

In the following sections the amygdaloid area elongates and the putamen and the putamen-internal capsule-caudate nucleus region is less important. The central nucleus becomes larger and contains several more or less separate collections of cells. The medial nucleus comes to have a fairly well defined cortex in which appears a definite prominence which probably represents the nucleus of the lateral olfactory tract (fig. 100). The medial nucleus is now confined to the ventricular surface and is soon replaced by the basal nucleus. Meanwhile the cortical nucleus occupies the surface lateral to the nucleus of the lateral olfactory tract.

Owing to the expansion of the general pallium since the stage of 175 mm. the whole temporal pole has undergone a rotation downward and inward so that the parts of the amygdala which were lateral in position in the earlier foetus are now basal or ventral in position and in a coronal series the medial, basal and lateral nuclei instead of lying side by side in a medio-lateral series, will be found in a series from above downward and the sections will cut one at a time.

In the next section shown (fig. 101) the basal nucleus occupies most of the front wall of the ventricle. Between it and the fused putamen-caudate is still the dense rounded mass which forms part of the central nucleus. The surface of the lobe is formed by the cortical nucleus and a remnant of the nucleus of the lateral olfactory tract. When the medial half of the basal nucleus is passed a section falls so exactly in the plane of the fiber-lamina between it and the lateral half that nearly the whole area of the basal nucleus appears devoid of cells. Following this appears the lateral half of the basal nucleus composed of somewhat larger cells and having a distinct L-shape, just as it appears in figure 85 from



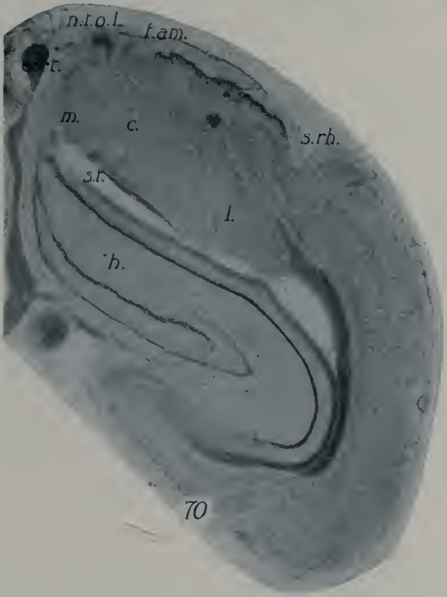


Fig. 69 Through the upper part of the optic chiasma. The diagonal band has fused with the central and medial amygdaloid nuclei. The fused putamen and caudate still occupy a considerable area. The lateral amygdaloid nucleus has appeared behind the caudate and is connected with the plate of cells along the external capsule. Immigration of cells appears at the medial border of the pyriform cortex (*f.am.*). The lateral olfactory tract is also marked by the letters *f.am.*

Fig. 70 Through the lower part of the optic chiasma. The sulcus hemisphericus separates the temporal pole from the hypothalamus. The place of the putamen has been taken by the lateral amygdaloid nucleus which has spread forward as far as the caudal border of the stria terminalis. Its lateral border shows many small clumps of cells which continue forward to the amygdaloid fissure where there is an active immigration of cells over a broad area. The central and medial amygdaloid nuclei are covered forward by the cortical nucleus and the nucleus of the lateral olfactory tract.

the 175 mm. foetus. The concavity of the L is filled by the lateral nucleus and between the two in both specimens appears a special dense clump of cells. This lateral basal nucleus is traversed lengthwise by coarse fibers which probably go in part to the cortical nucleus.

Before the basal nucleus has been passed the lateral nucleus makes its appearance as a number of apparently isolated plates or cords of cells lying between the bundles of corona radiata and anterior commissure bundles as they run toward the temporal cortex. These cell-plates are in reality the ridges or lobules of the surface of the lateral nucleus already described. In a later section the lateral nucleus appears as a wide area of small cells overlapped obliquely by the remnant of the larger-celled basal nucleus. This is almost the last section in which the fused putamen-caudate appears.

Below this level sections cut the lateral nucleus only. The lobulation on the side adjoining the corona radiata is well shown in figure 102.

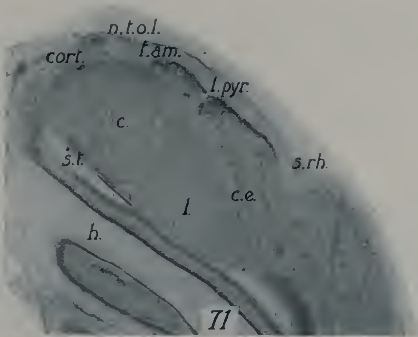
The course of the stria terminalis cannot be followed in detail in these sections, but the bundles to the medial, cortical and both parts of the basal nuclei are clearly seen.

Fig. 71 Eight sections below the last. The lateral nucleus occupies fully half of the amygdaloid area. The central nucleus is reduced and around it appear indistinctly plates of very small cells (intercalated masses). Immigration of cells is still evident at the fissura amygdalæ.

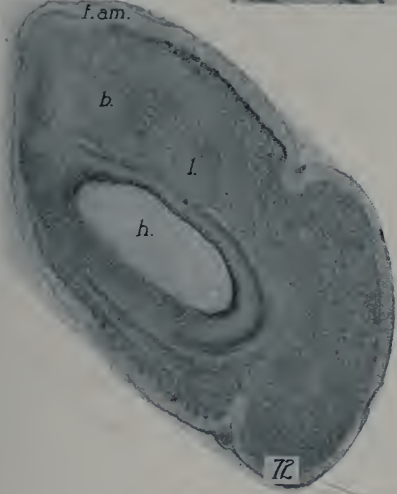
Fig. 72 Twenty sections below the last. The basal nucleus has replaced the central, and the lateral nucleus is much smaller. Note large-celled and small-celled parts of the basal nucleus. Cells appear to be migrating from the fissura amygdalæ into the basal nucleus.

Fig. 73 Eight sections below the last. The basal and cortical nuclei alone remain. The fissura amygdalæ ends in the medial wall, having crossed over the basal surface. Note the broad band of cells extending in to the basal nucleus.

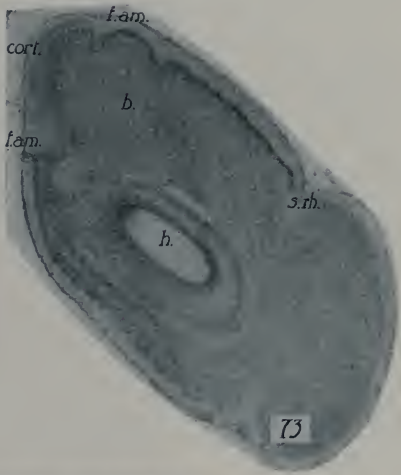
Fig. 74 Section through the fissura amygdalæ of the left side at a level corresponding to that of figure 70. The nucleus of the lateral olfactory tract appears at the right, the pyriform cortex at the left. The arrangement of cells shows that there has been an active migration of cells inward from the cortical layer at the fissure.


n.t.o.l.
cort.
f.am.
l.pyr.
c.
s.t.
s.rh.
c.e.
l.
h.

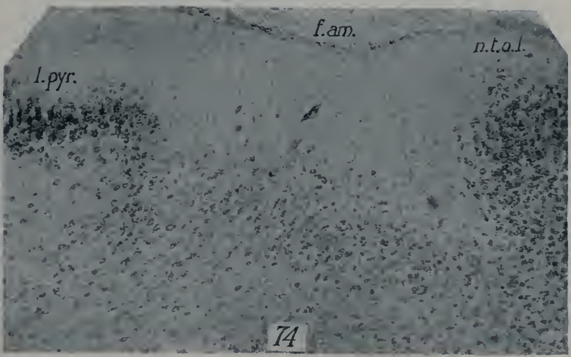
71


f.am.
b.
l.
h.

72


f.am.
cort.
b.
f.am.
s.rh.
h.

73

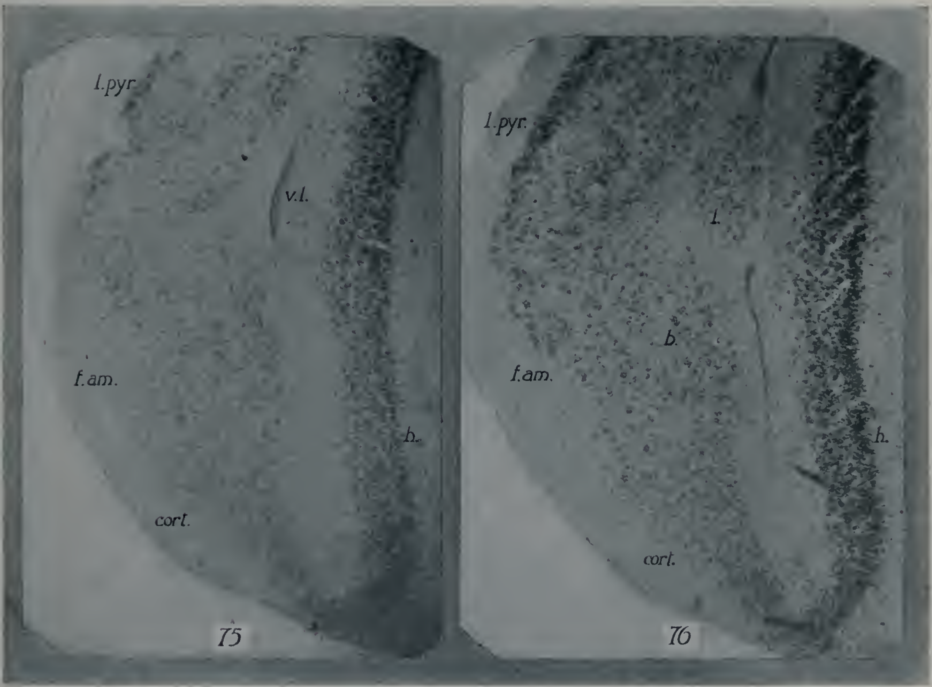

f.am.
n.t.o.l.
l.pyr.

74

d. Summary of the amygdala

The somewhat detailed review of the nuclei entering into the amygdaloid complex in a marsupial, mammals and man seems to show that there is essential uniformity in these structures. The same nuclei are present and in the same form and relative position. There is one nucleus, the accessory basal, in the opossum not separately recognized in mammals, while the small-celled and large-celled parts of the basal nucleus in mammals are distinctly separated by a lamina of fibers. The position of the nuclei is shifted in two respects. First, between marsupials and the lower mammals the nuclei which occupy the floor of the temporal horn in the opossum are shifted into the rostral wall of the ventricle by the elongation of the hemisphere and the turning downward and forward of the caudal wall of the temporal pole. Second, the nuclei which lie in the following transverse order in the lower mammals, medial-basal-lateral, are shifted in man into a nearly vertical series in which the medial nucleus is most dorsal (high up in the sulcus hemisphaericus) and the lateral nucleus is most basal.

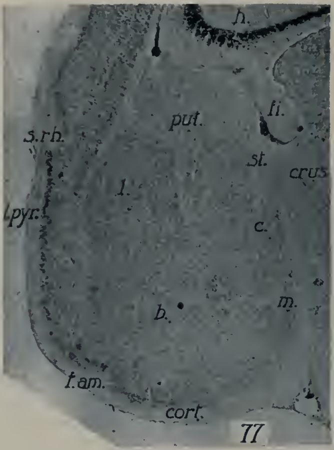
The nuclei fall into two distinct groups from the standpoint of origin and age: the primitive or little modified central, medial, cortical and nucleus of the lateral olfactory tract; and the new nuclei formed by infolding or immigration of cells: basal and lateral. The nucleus of the lateral olfactory tract is a remnant of the primitive lateral olfactory area of fishes which has been maintained as the place of ending of a part of the lateral olfactory tract and which in all vertebrates is connected with its fellow by a bundle of fibers through the anterior commissure. This nucleus is much reduced in primates, but is not wholly absent as Völsch believes. The medial nucleus is also a remnant of the olfactory area of lower vertebrates. It is not differentiated in the reptiles but in marsupials and mammals it appears as a special cell mass derived from the medial and superficial part of the lateral olfactory area. The central nucleus represents the deeper part of the olfactory area. The central and medial nuclei remain always in the closest relation and together give rise to the largest part of the great olfactory projection tract, connecting the amygdala with the hypothalamus. This tract is primitive and is large in fishes, namely that portion of the tractus olfacto-hypothalamicus which arises from the lateral olfactory area. Its course to the hypothalamus lies above and medial to the lateral forebrain bundle

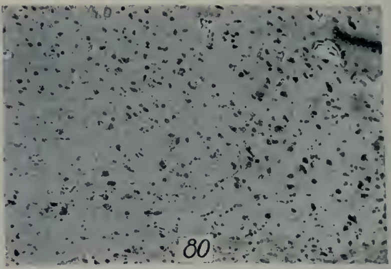


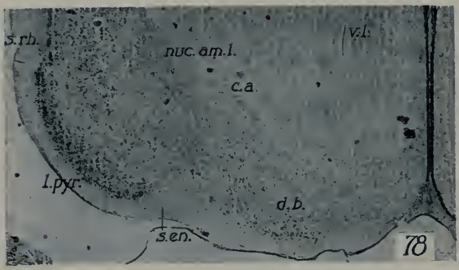
Figs. 75 to 79 Five transverse sections of the brain of the bat Myotis between the temporal pole and the precommissural region to show the relations of the nucleus of the diagonal band and the amygdaloid complex. The photographs are flat because the sections are very thin. Neutral red.

Fig. 75 Through the caudal part of the temporal pole. × 110. The fissura amygdala is marked not by an external groove but by a broad arching inward and thickening of the cell layers. Note the contrast with the pyriform cortex. The ventricle is a narrow cleft in the bat. This photograph and the next are rotated clockwise in placing on the plate. A line passing through *f.am.* and *v.l.* and one through *f.am.* and *l.* in figure 76 would be parallel with the median vertical plane of the brain.

Fig. 76 Section 0.1 mm. rostral to the last. × 110. Continuation of the broad in-folding of cells forming a fairly distinct basal nucleus. The lateral nucleus appears as a small triangle pushing into the ventricle from the lateral side and nearly obliterating it.







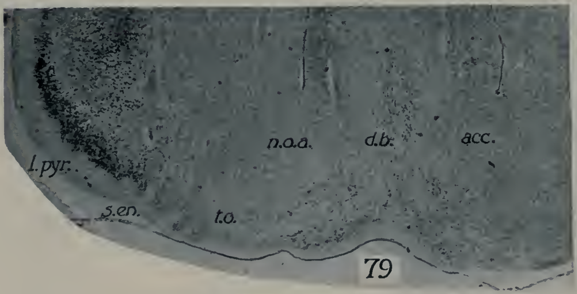


Fig. 77 Section at the caudal border of the internal capsule. × 50. The stria bed descends medial to the putamen and expands into the central and medial nuclei. The basal nucleus occupies a broad area made up of irregularly scattered clumps of cells. It is covered by a broad cortical nucleus. The lateral nucleus stands up as a great triangular mass between the putamen and the pyriform cortex.

Fig. 78 The diagonal band is seen near the basal surface, its large cells rising up toward the anterior commissure. Lateral to it is the sulcus endorhinalis at about

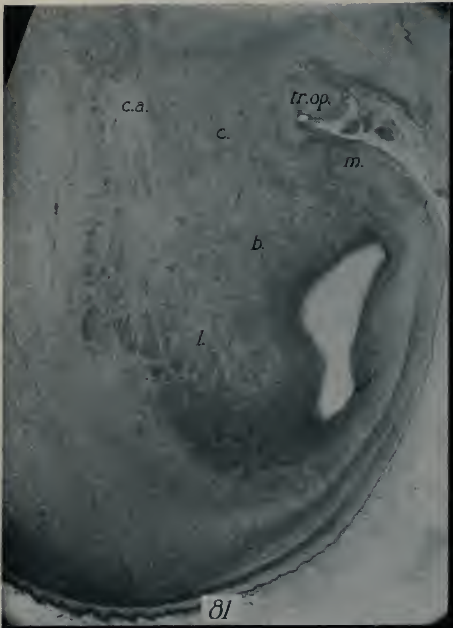
which connects the general somatic sensory centers in the thalamus with the primitive general pallium in the forebrain. The movement of a part of the lateral olfactory area backward into the caudal pole and downward into the temporal pole of the hemisphere has caused this tract to arch over the thickened lateral forebrain tract (internal capsule) as part of the stria terminalis. The central nucleus, although not clearly recognized by previous authors, is always a well defined large mass of small and medium sized cells which form a bed through which all the bundles of the stria terminalis spread apart to go to their several nuclei. It also continues forward as a large mass beneath the internal capsule and globus pallidus and beneath the anterior commissure until it merges insensibly with the deep gray of the diagonal band.

The cortical nucleus is in part a product of the amygdaloid involution. It is formed from the cortical layers of the pyriform lobe medial to the sulcus endorhinalis. In marsupials, it seems to be formed by migration of cells inward while a cortical layer persists, comparable to the pyriform cortex lateral to the sulcus endorhinalis. In mammals this cortical layer is more vague as it is more or less completely used up in forming a massive superficial nucleus with irregularly placed cells. Thus the cortical nucleus has not taken on a new position due to the infolding but has been modified in structure by secondary proliferation (growth) and in-wandering of cells.

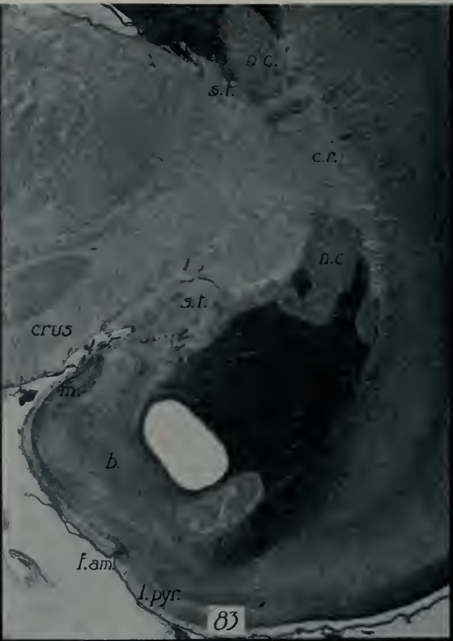
the foremost level at which there is an active immigration of cells to form amygdaloid nuclei. Internal to the sulcus the gray area between the pyriform cortex and the diagonal band cells represents the undifferentiated area which is submerged at this level as described in the text (p. 430).

Fig. 79 A short distance rostral to the last, passing through the caudal part of the tuberculum olfactorium. The nucleus of the diagonal band rises well up in the medial wall. Note the anterior olfactory nucleus and nucleus accumbens, a single body as in other forms. The lateral olfactory area is superficial again medial to *s.en.* and fuses with the tuberculum.

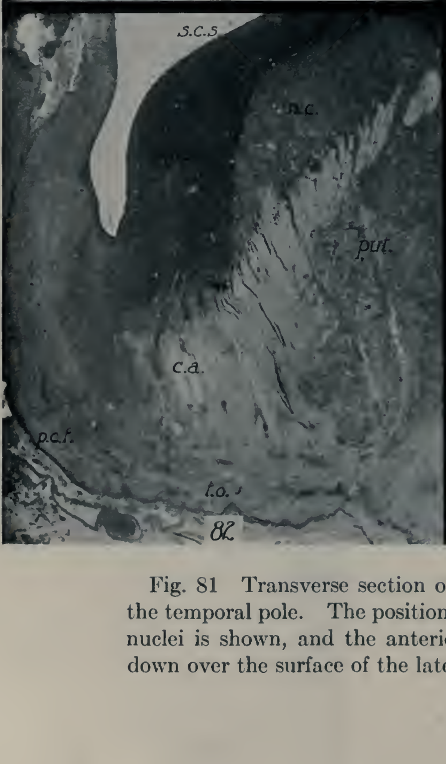
Fig. 80 Transverse section through the globus pallidus of the telencephalon of the turtle, Cistudo carolina. The location of the large cells here shown may be seen by comparing figure 18. Cells corresponding to these appear in that figure as small clumps imbedded among the crus fibers.



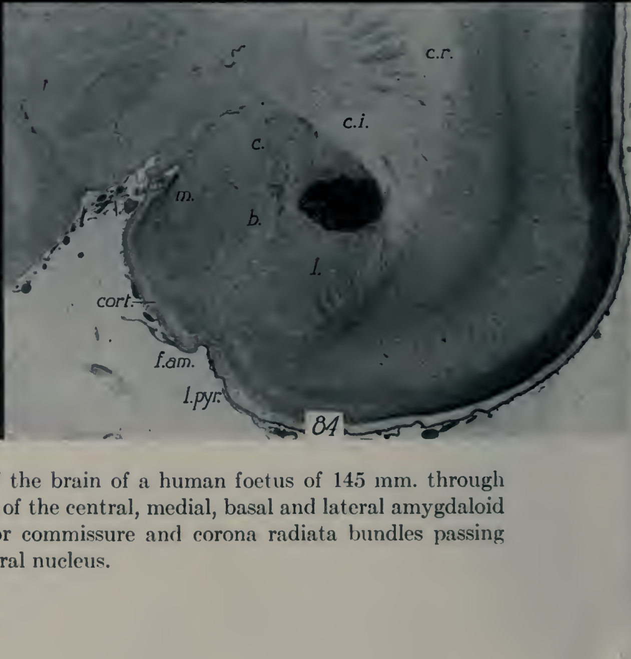
81



83



82



84

Fig. 81 Transverse section of the brain of a human foetus of 145 mm. through the temporal pole. The position of the central, medial, basal and lateral amygdaloid nuclei is shown, and the anterior commissure and corona radiata bundles passing down over the surface of the lateral nucleus.

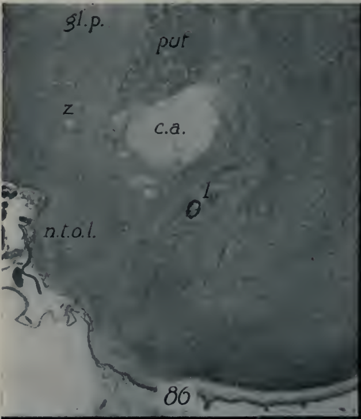
The formation of the amygdaloid ridge in the turtle is due to a broad infolding of lateral olfactory area on the ventro-lateral aspect of the temporal pole, along the line of the endorhinal fissure. In this sense the substance of the central and medial nuclei has been involuted, carried deeper into the brain, but this was a translocation merely. In addition to that there has occurred a secondary hypertrophy of the cortical layer adjacent to the sulcus endorhinalis and a migration of cells inward to form the great basal and lateral nuclei of the amygdala. The first step in this produced the large-celled nucleus which has a medial position in the turtle. It must be remembered that this nucleus lies not in the medial wall of the temporal horn of the ventricle but in the medial part of the amygdaloid ridge. The medial wall between this nucleus and the bed of the stria terminalis forward is the locus of the medial nucleus of mammals. The large-celled nucleus probably owes its origin to the involution of part of the pyriform cortex. In the rabbit the cells of this nucleus bear a striking resemblance in size, form and staining reaction to the cells of the pyriform cortex. Many of them are double pyramids and they may be regarded as cells of the same type that form the double pyramids of the pyriform cortex. In addition to the large cells the basal nucleus contains small cells which form a large part of its volume. In Erinaceus and Mus Völsch does not mention the large-celled nucleus, while in Foetorius, Lemur and Macacus he describes distinct large-

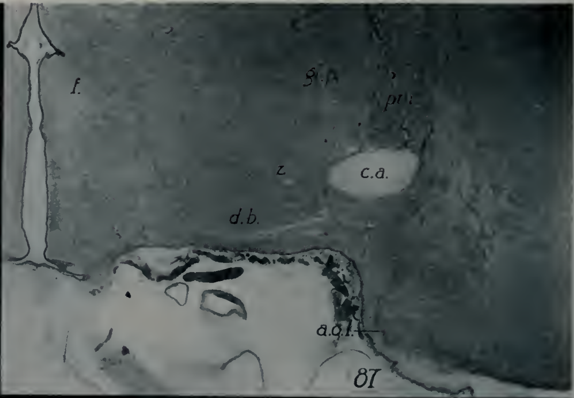
Fig. 82 Transverse section of the brain of a human foetus of 145 mm. C.R. at nearly the same level as figure 90, H. 2 J. 55. × 10.5. The precommissural fiber system is prominent. The stria bed extends down medial to the anterior commissure bundles toward the tuberculum. Note the cords of darkly stained cells stretching down from the ventricular layer of the stria bed.

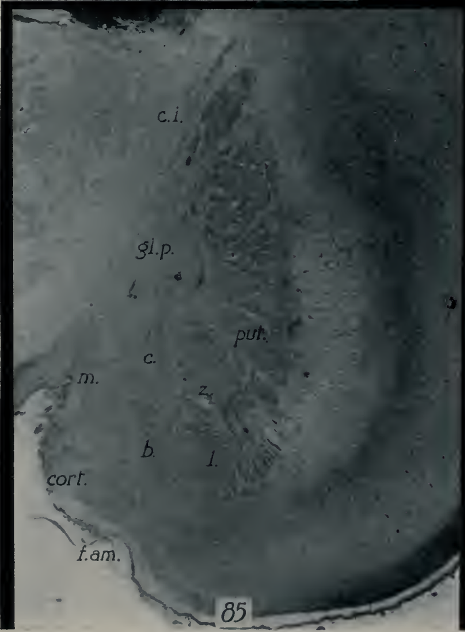
Figs. 83 to 90 Transverse sections of the telencephalon of a human foetus of 175 mm. C.R. H. 27 J. × 6.

Fig. 83 Near the caudal border of the internal capsule. Below the capsule the stria bed is expanding to form the medial and central nuclei. Basal and lateral nuclei appear beneath the ventricle. Note the fan-like spreading of stria fibers medial to the ventricle.

Fig. 84 Section 0.75 mm. forward from the last. Note the large central nucleus, the twin basal nuclei and the massive lateral nucleus. Intercalated masses are conspicuous.







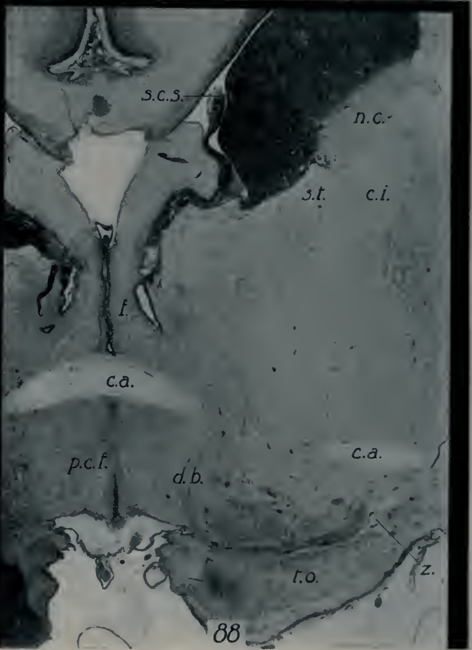


Fig. 85 Section 0.45 mm. forward from the last. The large putamen and globus pallidus now occupy a good part of the section. The central nucleus is still large. Ventro-laterally it is covered by a capsule of fibers going out from the amygdala forward. This is where the two bundles like the sign ( ) appear in other animals. The basal nucleus is still divided by a lamina of fibers. The lateral nucleus is reduced. A small bundle of fibers marked *z* in this and the following figures is traced to the tuberculum olfactorium.

celled and small-celled nuclei. In the opossum, rabbit, Macacus and man I find the two parts distinct, while in the bat the large cells are somewhat intermingled with the small cells. Even here the large cells are in the deeper part of the nucleus as in the opossum. In higher mammals, as a result of the turning downward and inward of the temporal pole due to the expansion of the general pallium, the two parts of the basal nucleus have been rotated so that the large-celled part comes to lie lateral to the small-celled part, and next to the lateral nucleus. Finally in man the rotation has gone farther, so that the lateral structures become basal with reference to the medial nucleus and the small-celled part of the basal nucleus.

The evidence from the opossum, rabbit, bat and human foetal brains seems to show that both parts of the basal nuclei have been formed from the posterior part of the area of infolding and immigration along the sulcus endorhinalis, while the lateral nucleus has come from the anterior part of that area. This is especially clear in the bat and the strands of cells in the rabbit and man leading from the involution area to the anterior border of the lateral nucleus are corroborative evidence. There is, however, a very sharp difference in the mode of formation of the basal and lateral nuclei and in the position which they take up with reference to older structures. In the caudal region (see especially figures of the opossum) the fiber layer of the external capsule from the lateral wall meets with the stria terminalis bundles from the medial wall in a continuous sheet across the base of the temporal pole. The basal nuclei cause a thickening of the basal wall

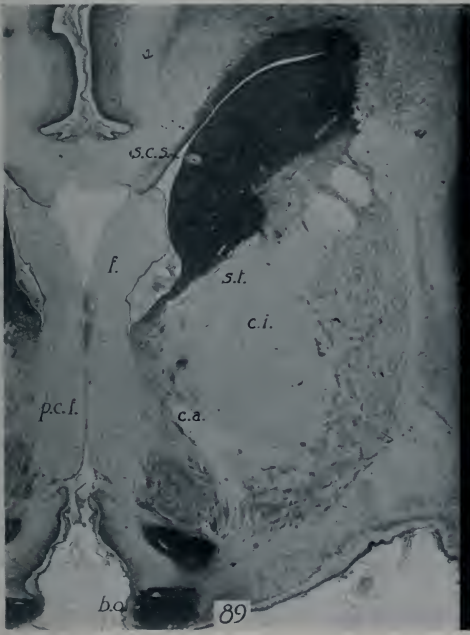
Fig. 86 Section 0.95 mm. forward from the last. The section shows the temporal limb of the anterior commissure with six small bundles accompanying it (system *y*). Beneath the commissure are several clumps of cells belonging to the lateral nucleus. On the medial surface is the small nucleus of the lateral olfactory tract.

Fig. 87 Section through the preoptic recess, 0.7 mm. forward from the last. This shows the small bundles of the last figure (*y*) traversing the diagonal band toward the precommissural fiber system. Here the bundles become diffuse and cannot be traced further. The bundle *z* remains distinct.

Fig. 88 Section through the anterior commissure 1 mm. forward from the last. The small bundle *z* descends into the tuberculum. Stria bed and nucleus caudatus are quite distinct.

and push this fiber layer up on their deep or internal surface, so that it comes to lie between them and the central nucleus. In this region is found an extensive and complex network of fibers, of which the 'sagittales Längsbundel' is part, all of which may be regarded as in a sense a modification of the external capsule. The basal and cortical nuclei remain as a thickening of the basal wall outside of the external capsule. Farther forward, where the anterior commissure enters the external capsule, the cells wandering in from the line of the sulcus endorhinalis took up a position on the internal face of the external capsule between it and the putamen. Here the cells moved upward and backward until the greater part of them occupied a ventricular position behind the putamen as the thick lateral nucleus (opossum, rabbit, bat). This is essentially the position of the lateral nucleus in earlier human foetuses, but in later stages it is carried into a more basal position, as already described. Because of its mode of formation the lateral nucleus comes to be covered over its whole lateral face by the external capsule and it is more closely related to the putamen than the other nuclei are.

When we look for an explanation of this morphological history of the amygdaloid complex in the habits and environment of animals and the functions to be performed, we will find it helpful to reduce the story of its evolution to still more general and broader lines. The formation of the hemisphere, which remains to be discussed later, resulted in bringing an important part of the lateral olfactory area into the temporal pole. This temporal olfactory area was connected with the anterior olfactory nuclei, 1) along the lateral surface of the hemisphere by the elongated lateral olfactory area in which ran the lateral olfactory tract; 2) by a basal area containing the equivalent of the diagonal band, anterior perforate space and the tuberculum olfactorium, and, 3) along the ventricular surface by the deep counterpart of the lateral olfactory area in which ran the commissural bundle and other fibers which we now assign to the stria terminalis. As the expansion of the general pallium pushed the temporal olfactory area farther apart from the anterior olfactory areas, the thickening of the internal capsule caused an arching up and reduction in volume of the middle part of the gray bed of the stria terminalis. There was then a fairly massive temporal area receiving the endings of the lateral olfactory tract and connected with the anterior olfactory areas and other brain centers by fibers running in the stria terminalis, the diagonal band and the stria medullaris. This is the general situation which we designate by the term, the amygdaloid area.



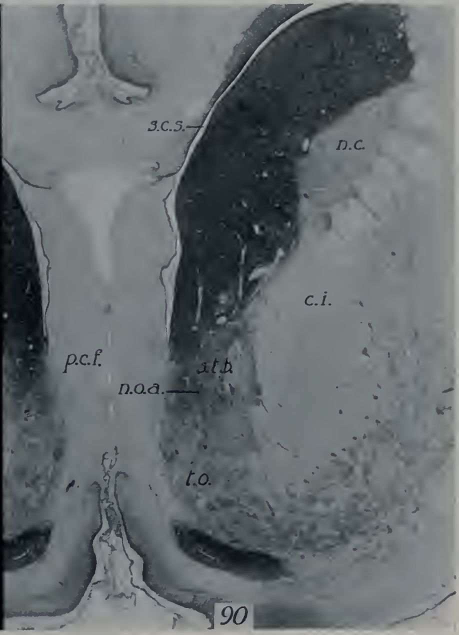
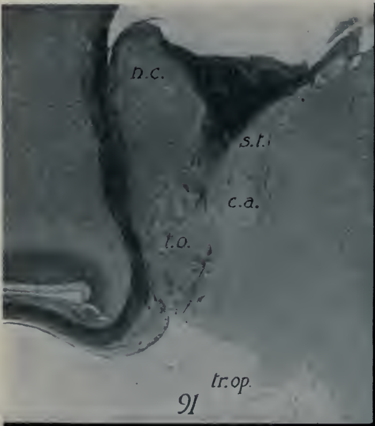
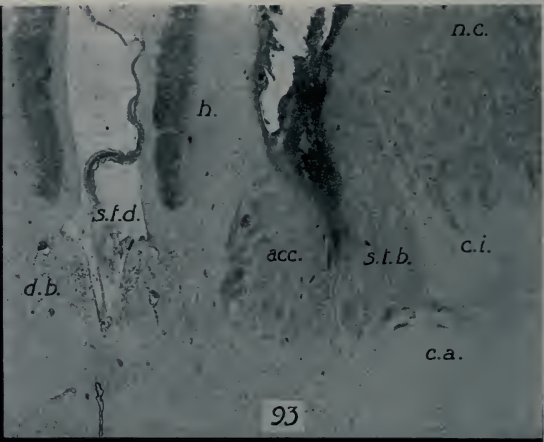
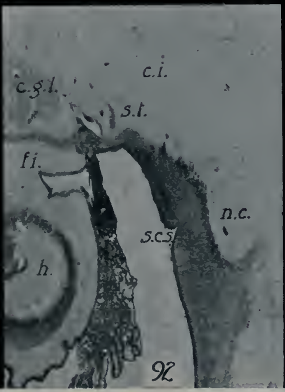


Fig. 89 Through the base of the olfactory peduncle showing the distribution of the anterior limb of the anterior commissure. Note the very thick ventricular layers overlying the stria and the caudate. The stria bed descends between the anterior commissure and the precommissural fiber-system toward the tuberculum. The strio-caudate sulcus is homologous with the middle ventricular sulcus of the turtle (cf. figs. 17, 18).

Fig. 90 Section 0.8 mm. forward from figure 89. This section shows clearly the independence of the stria bed from the caudate nucleus. Here the stria bed extends from the letters *s.t.b.* to *s.c.s.* Below *s.t.b.* it fuses with the anterior olfactory nucleus which lies upon the tuberculum. Note the large island of the tuberculum extending up in the medial wall and compare with a corresponding section in the opossum, figure 60.







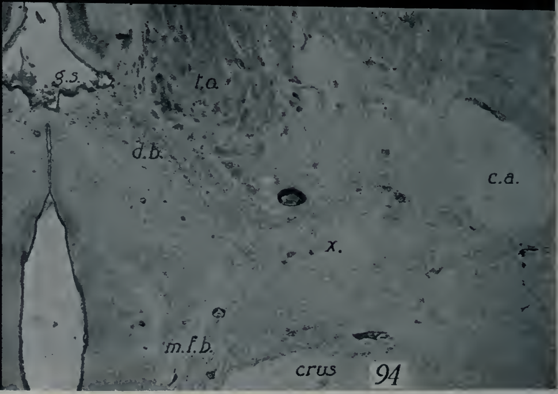


Fig. 91 Parasagittal section of the brain of a human foetus of 200 mm. C.R., in the region of the olfactory peduncle. H. 24 J. × 6. Description in text (p. 351).

Fig. 92 Coronal section of the region of the choroid fissure in the hemisphere of a human foetus of the eighth month. H. 26 J. sec. 140. The section shows the stria terminalis as it descends over the caudal surface of the internal capsule. Laterocaudal to it is the tail of the caudate nucleus. Both are covered by a deeply staining ventricular layer of cells. This layer is indented by a small but sharp strio-caudate sulcus. Among the stria bundles are several small collections of cells. Small portions of the hippocampus and the lateral geniculate body are included in the figure.

Figs. 93 to 102 Ten coronal sections of the brain of a human foetus of the eighth month to show the relations of the nucleus of the diagonal band and the amygdaloid complex. Neutral red. H. 26 J. The magnification is × 9 except as noted. Owing to the low magnification the cell masses appear as merely gray areas. The large cells of the diagonal band show as black dots. The sections are fully described in the text.

This seems to be the condition reached in the amphibians and no higher specialization is needed to provide for the more intimate association of the senses of taste and smell due to the opening of the olfactory sac into the mouth, which is discussed at length by Herrick ('21). Since these functions are cared for by the simple form of amygdala found in the amphibians, the relation to the vomeronasal organ would in no great degree condition the further evolution of the amygdala in higher forms.

In studying the differentiation of the amygdala in reptiles and mammals, then, we start with a primitive form of amygdala whose location in the temporal pole was brought about by the expansion of the general pallium and the mere fact of the formation of the temporal pole. This primitive amygdala has undergone modifications and has received additions on account of the complex conditions resulting from the terrestrial mode of life. An animal living on land is subjected to a much wider range of stimuli and to much greater and more sudden changes of its conditions of life than is an animal living in water. The temperature may rise higher and fall lower and the change of temperature in a single day on land may be much greater than animals in water would experience in a year. Variation in temperature and in moisture content of the medium of life which have brought about the evolution of hair and glands have not been without significance in the evolution of the correlating mechanisms in the nervous system. The change in the mode of respiration has affected not only the circulatory and other visceral organs but the muscles and skeleton as well. The air not only replaces water as the medium of respiration but also as the medium through which important sense organs must receive their impressions. First of these is the distance receptor

Fig. 93 Below the anterior commissure. × 12. The relations of the stria bed, nucleus accumbens and diagonal band are the same as in the opossum and rabbit.

Fig. 94 Near the brain base where the diagonal band bends caudo-laterally. Between the anterior commissure and the tuberculum are seen several bundles (system *y*) which follow the anterior commissure to the pyriform lobe. The course of these bundles toward the precommissural region is better shown in figures 86 to 88. Some of these bundles doubtless end in the tuberculum olfactorium. The hypothalamic bundles faintly shown at *x* are better seen in the following figures.

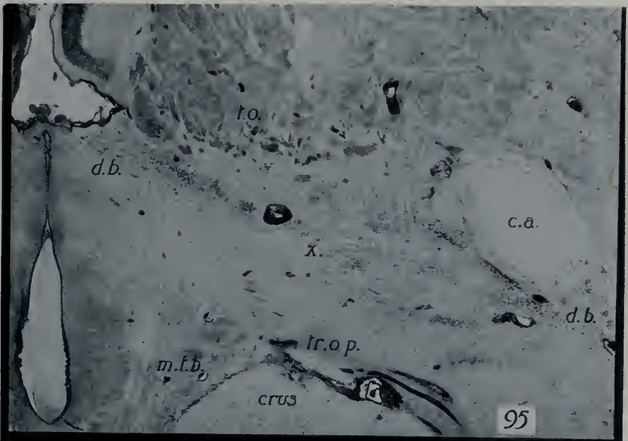
in the search for food, the olfactory organ. The olfactory sense cells must still receive their direct stimulation through the moisture that bathes the mucosa, but the minute emanations from distant objects which are detected by the olfactory cells must be carried to them by diffusion through air or by air currents. The olfactory mucosa was already depressed in a nasal sac in fishes and this position has been retained in land animals because of the necessity of keeping the surface moist. The opening of the nasal sac posteriorly into the pharynx made it possible for the respiratory air currents to serve the sense of smell.

The air also is vastly superior to water for the transmission of both sound and light. Some fishes are stimulated by a restricted range of sound waves, but these rapid vibrations impinge on the ear of land animals constantly and with so much greater intensity that the ear is modified into essentially a new organ to serve the function of hearing, one of the most important means of information about the environment. Whereas in fishes connections of the acoustic centers with correlating centers in the forebrain are unknown, the auditory apparatus in land animals commands a large place in the great organ for correlation of all sense impressions, the pallium. Likewise vision, although important in fishes, becomes vastly more complex, deals with more numerous, more varied and more distant objects, its organ must be adapted to great changes in intensity of light, and the visual system plays a greater part in both the reflex and voluntary activities of land animals than in fishes.

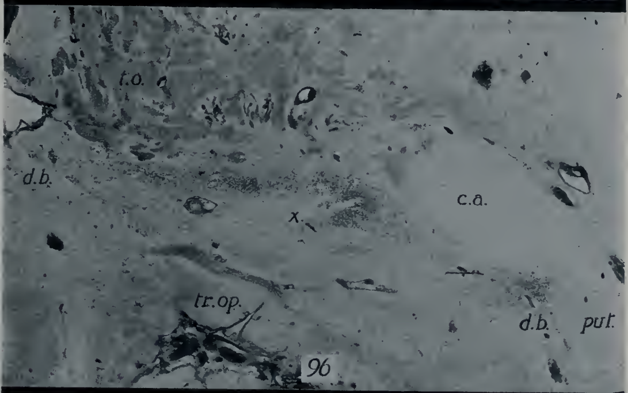
Fig. 95 A little (1.8 mm.) lower than the last section showing the medial forebrain bundle and the spreading of the nucleus of the diagonal band beyond the temporal limb of the anterior commissure. At the right hand edge of the photograph this nucleus meets the putamen. The bundles x are fully described in the text (p. 379).

Fig. 96 A few sections (0.12 mm.) below the last. The contact of the diagonal band nucleus with the putamen is seen here. The volume of this nucleus and the great number of large cells which it contains can be appreciated from these photographs. Diagonal band cells are seen above the anterior commissure. Also it is evident that the bundles x form a system of some importance.

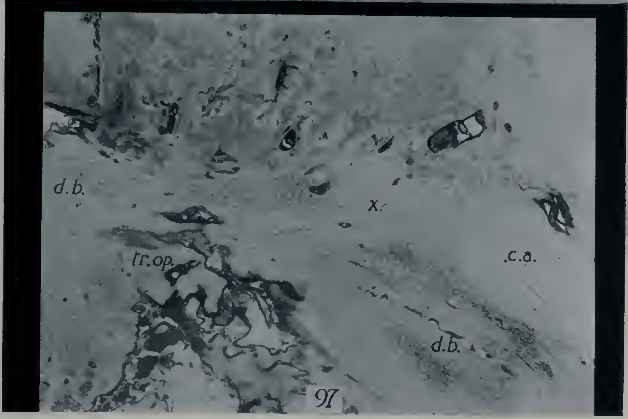
Fig. 97 Very near the basal surface, 0.15 mm. below the last section. Note the large masses of diagonal band cells beneath the anterior commissure.



95



96



97

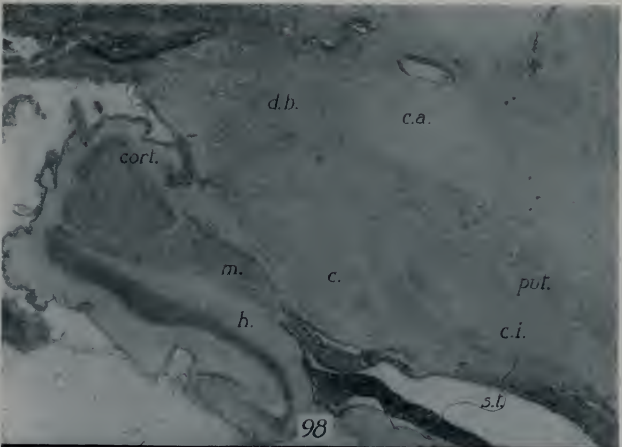
Furthermore, the conditions of life on land brought about a great increase in the number and complexity of the impressions received through the tactual and proprioceptive systems. Fishes are completely bathed with water and free-swimming forms seldom come into contact with solid objects except when they grasp food with their mouths. Land animals in their search for food and manifold other activities are in constant touch with the ground and the vegetation, with their shelters, their fellows and their enemies. Myriad contact impressions of unending variety are reported to the brain and have demanded for their correlation the great development of the touch center in the pallium.

Similarly the complex activities of the land animals have required the development of elaborate mechanisms of skeleton and muscles for locomotion, for securing food, for building shelters and so on. For the control of these organs every muscle must be supplied by numerous sense-fibers and impressions received from the actions of the muscles must be carried to the pallium for correlation with tactual, visual and auditory impressions. Per-

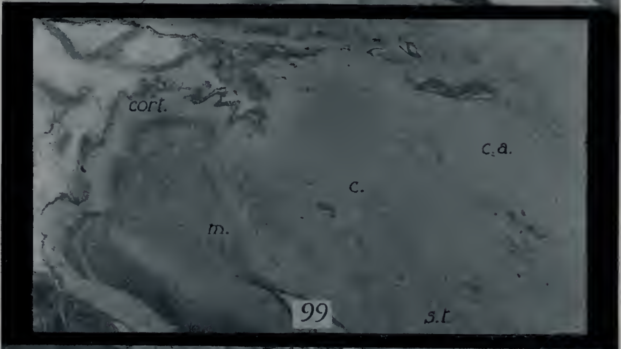
Fig. 98 Section through the temporal pole 0.7 mm. below the level of figure 97. The section cuts the lower border of the putamen and the lowermost bundles of the internal capsule. The very small tail of the caudate lies below the edge of the photograph at the right. Clusters of diagonal band cells are seen medial to the anterior commissure and in contact with the putamen. The bed of the stria terminalis inclines forward along the wall of the ventricle and joins the large central amygdaloid nucleus (*c*). The medial nucleus at this level appears to be separate from the central and more nearly related to the hippocampus. This is due to the rolling under of the temporal pole. Later sections show that the alveus (*h*) marks the dividing line between hippocampus and amygdala in this section.

Fig. 99 Section 0.2 mm. below the last. Part of the stria is left out of the photograph below. The large bundle between the central and medial nuclei corresponds to the bundle in the opossum and rabbit which follows along the ventricle to reach the basal and cortical nuclei. The nucleus of the diagonal band is represented by one cluster of cells near the anterior commissure bundle.

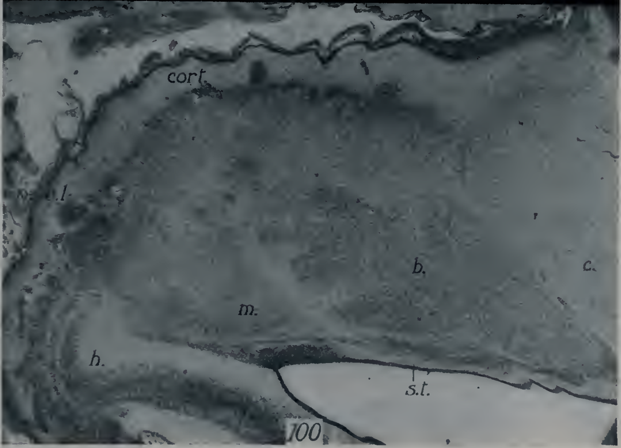
Fig. 100 Section 0.8 mm. below the last. × 13.3. The anterior commissure and the lowest angle of the fused putamen-caudate are left out of the photograph to the right. The section cuts the lower borders of the central and medial nuclei and the upper part of the basal nucleus which lies below the other two. Stria terminalis fibers run along the ventricular surface of the nuclei. The cortical nucleus is extensive and shows folding of its cell layer similar to that of the anterior perforate space and tuberculum olfactorium. Dense clumps of cells overlying the medial nucleus at the left represent the nucleus of the lateral olfactory tract.



98



99



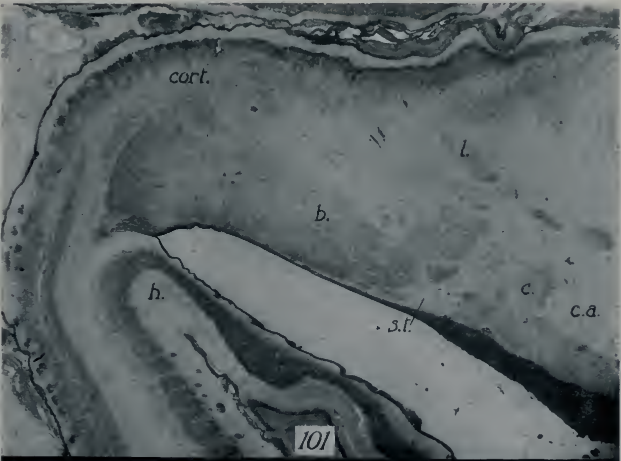
100

haps the largest of all the sensory areas of the pallium is devoted to this function.

Finally, the significance of the sense of smell has been changed. With the development of the other sense organs the sense of smell became less important in the search for food and became more important as a means of protection against deleterious conditions which might be indicated by odors. Finally, in man olfactory impressions have come to have considerable aesthetic value, giving pleasure or displeasure aside from any material service in maintaining life.

All this and more we imply in speaking of the expansion of the general pallium in terrestrial vertebrates. The forebrain of fishes had a large apparatus for olfactory impressions and for the correlation of these with taste impressions. It had also a considerable area for the reception of at least tactual and visual impressions and means for the correlation of these with olfactory impressions (fiber connections between somatic and lateral olfactory areas). Since there is a large lemniscus system in fishes bringing proprioceptive impulses up to the thalamus, it is probable that these are represented in the thalamic radiations to the somatic area in the forebrain. The needs of land animals brought about the expansion of the tactual, proprioceptive, visual and motor elements and the addition of an auditory element to the somatic pallium. The visual and auditory elements were located in the caudal part and with the final development of border zones and association areas these were pushed into the occipital and temporal poles, respectively.

Now, throughout all these changes in habits and activities on one hand and in brain structure and functions on the other we are interested here in the relations of the olfactory mechanisms to the greatly enlarged somatic pallium having to do with the external relations of the organism to its environment. We have seen that the olfactory centers in the medial wall of the hemisphere have greatly diminished from selachians to land animals, while the lateral olfactory area has developed in relative size and complexity, giving rise to the pyriform lobe as an organ for correlation with the somatic pallium. The morphological evo-



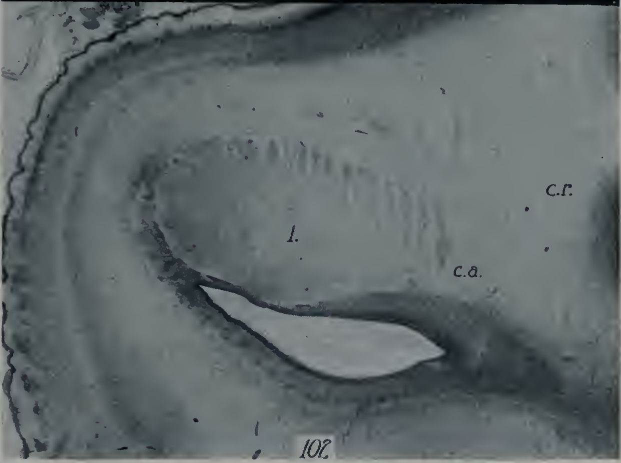


Fig. 101 Section 1.5 mm. below the last. The section cuts through the length of the basal nucleus. A remnant of the central nucleus is seen near the anterior commissure. Strands of stria and other fibers traverse the basal nucleus to reach the cortical nucleus and pyriform cortex (compare figures 26, 41, 42). The lateral nucleus is represented by clumps of cells which are in reality the tips of the lobules cut off (compare figs. 81, 84, 85, 102).

Fig. 102 Section 2.3 mm. below the last. The section is near the end of the temporal horn of the ventricle. The nucleus (*1*) which is distinctly lateral in position in marsupials and mammals is the most basal in man. Note how the anterior commissure bundles cut into and lobulate the lateral nucleus as they enter the corona radiata and spread to the temporal cortex.

lution of the amygdaloid complex shows that it consists of two parts: the central and medial nuclei constituting an old part which is connected with the medial olfactory nuclei, the hippocampus and the hypothalamus; and the basal, lateral and cortical nuclei which are newly added or enlarged by infolding and proliferation of the pyriform lobe. The connections of the medial and central nuclei indicate that they are concerned with olfactory functions and olfacto-gustatory correlation. They give rise to the chief olfactory projection tract.

The newly formed nuclei appear to be for the most part an expansion and further differentiation of the olfacto-somatic correlation area, the pyriform lobe. This lobe is related to the whole lateral border of the general pallium including the occipital pole and medial wall up to the hippocampus. Throughout this whole extent there is a rich interchange of short and longer association fibers. Also by way of the external capsule and the anterior commissure the pyriform lobe may be brought into connection with distant cortical areas in the same and opposite hemispheres. The odors borne by the air are the source of so many and varied forms of information or clues regarding the environment of a land animal, not only with reference to food but with reference to all its external relations, that the expansion of the pallium for correlation of tactual, visual, auditory and proprioceptive impressions with one another demands a coördinate development of centers for the correlation of all these with olfactory impressions. The lateral olfactory area, although it elongated pari passu with the general pallium, was not equal to this task without further development and differentiation. Already in reptiles it began at the same time with the general pallium the process of increasing surface by folding. The first examples of this were the infolding of the dorsal ventricular ridge (caudate nucleus) as an accession to the pallium and the infolding of the basal amygdaloid nucleus as an accession to the pyriform lobe. In mammals the general pallium further increased its surface by many folds of the cortex, and the pyriform lobe by further immigration of cells to form lateral and cortical amygdaloid nuclei.

These new nuclei show an increasing disjunction from the primitive type of connections of the amygdala. While the basal nucleus preserves a bundle in the stria terminalis connecting with the parolfactory area and hypothalamus, it is also connected with the pyriform lobe by a rich network of its deep association fibers. The lateral nucleus has no single well-defined tract of afferent or efferent fibers. It in common with the pyriform cortex itself shares in the distribution of the hypothalamic bundle which enters into the amygdalo-pyriform association bundle. Its chief connections, however, are by way of the last-named association bundle, the external capsule, and fibers to the putamen. Its chief connections, therefore, are with somatic centers or olfacto-somatic correlation areas. The lateral nucleus represents the last step in olfacto-somatic correlation.

The task of unraveling and describing in detail the connections of each of these nuclei is one for more refined methods than I have used, especially for experimental methods. It is believed, however, that the foregoing analysis of the amygdaloid complex and the tracing of the evolution of its parts give a clear conception of the functional significance of the whole complex and of the chief differences in the functional relations of its parts.

SUMMARY OF RESULTS

1. The corpus striatum consists of, *a*) the bed of the stria terminalis, *b*) the lentiform nucleus, and, *c*) the caudate nucleus.

2. The bed of the stria terminalis is a part of the ancient olfactory centers and maintains the continuity of the olfactory nuclei in the temporal region with those in the parolfactory region. It consists essentially of the ventricular layer of the primitive lateral olfactory area.

3. The lentiform nucleus consists of putamen and globus pallidus, both of which are present in reptiles. The corresponding cell-masses are present also in selachians, where they have previously been described by the writer under the name of the somatic area.

4. The caudate nucleus appears first in reptiles as an ingrowth from the lateral border of the general pallium (dorsal ventricular

ridge). There is some indication of its beginning also in dipnoans. The caudate nucleus represents the first large increase of the somatic pallium by folding due to the increased demands made upon the pallium by the environment and habits of land animals.

5. Rostrally the bed of the stria terminalis includes that part of the head of the caudate nucleus, as heretofore understood, which is closely related to the nucleus olfactorius anterior and the nucleus accumbens.

6. The basal cortical area in selachians gives rise to the tuberculum olfactorium, the anterior perforate space and the diagonal band in reptiles and mammals.

7. The anterior perforate space is a continuation of the tuberculum olfactorium caudad but less highly differentiated.

8. The diagonal band consists of an elongated mass of gray matter and of important and complex fiber systems. The nucleus of the diagonal band is in contact with the hippocampus at the region of the neuroporic recess, occupies the gyrus subcallosus or its equivalent, and spreads latero-caudad in the brain base beneath the limbs of the anterior commissure, comes in contact with the putamen and merges insensibly with the central and medial nuclei of the amygdala.

9. The fiber systems of the diagonal band include interconnecting fibers between the amygdaloid complex and pyriform cortex on the one hand and the tuberculum olfactorium, parolfactory area, hippocampus and hypothalamus on the other. These fiber systems will well repay further study. The bundles to the hypothalamus should perhaps be regarded as crossing through the diagonal band rather than as belonging to it.

10. The fiber bundles constituting the stria terminalis in the opossum are summarized on page 381 and in figure 20. The stria of mammals and man has a similar constitution.

11. The olfactory projection tract represents the larger part of the lateral tractus olfacto-hypothalamicus of fishes. It is connected with the oldest part of the amygdaloid complex and may serve as an effective tract for the amygdala and for correlation of gustatory with olfactory centers.

12. The commissural bundle connects the nuclei of the lateral olfactory tracts through the anterior commissure in all classes of vertebrates.

13. The stria medullaris bundle connects with the nucleus of the lateral olfactory tract, the tuberculum olfactorium, the hippocampus and the pyriform cortex and represents the olfacto-habenular tracts and the posterior pallial commissure of lower vertebrates.

14. Other bundles connect the amygdala with the parolfactory area and the hypothalamus.

15. The bed of the stria terminalis expands caudad into the central and medial nuclei of the amygdala.

16. The amygdaloid complex consists of six or more cell-masses or nuclei, some of which represent the ancient olfactory area of fishes while others are new centers formed in the land animals by processes of growth, cell-migration and folding in the pyriform lobe.

17. A part of the primitive lateral olfactory area is maintained as the nucleus of the lateral olfactory tract. This becomes of less importance in higher mammals and is very small in the brain of the monkey and man.

18. Adjacent parts of the primitive lateral olfactory area are maintained in comparatively simple form and relations as the medial and central amygdaloid nuclei. The medial nucleus remains in superficial position and lies in the sulcus hemisphaericus next to the caudal end of the hippocampus. Its chief fiber tract is part of the olfactory projection tract.

19. The central nucleus is carried into a deep position immediately beneath the lentiform nucleus and internal capsule by the hypertrophy and folding which gives rise to the new nuclei. The central nucleus is the most direct avenue of continuity with anterior olfactory areas through both the bed of the stria terminalis and the diagonal band. Its chief fiber tract is the olfactory projection tract, but it has fiber connections with the pyriform cortex and possibly with the lentiform nucleus.

20. The cortical nucleus is derived from a part of the primitive olfactory area lying caudal to the nuclei thus far mentioned. In

this area the brains of mammals show hypertrophy and immigration of cells. All the nuclei above named lie to the medial side of the sulcus endorhinalis.

21. The sulcus endorhinalis marks the line of separation between the lateral olfactory area and the basal area (tuberculum olfactorium, etc.) in selachians. With the enlargement of the hemisphere and consequent elongation of these two areas the sulcus endorhinalis becomes an important landmark running lengthwise of the basal surface of the hemisphere in the midst of the pyriform lobe and parallel with the sulcus rhinalis which bounds the pyriform lobe laterally, separating it from the general pallium. The sulcus endorhinalis is followed by a large bundle of the lateral olfactory tract which is being distributed to all parts of the pyriform lobe.

22. In the caudal part of the elongated pyriform lobe the sulcus endorhinalis becomes the site of the active proliferation and in-wandering of cells and of actual folding of the brain wall. This part of the sulcus is therefore given the name fissura amygdalæ. This fissure is a large and prominent in-folding in reptiles and in all mammals including human embryos is a conspicuous feature of the amygdaloid region.

23. The in-folding of the fissura amygdalæ in reptiles has produced a ridge in the caudal part of the lateral ventricle which is small in turtles but large in lizards and some other reptiles. It is essentially an amygdaloid ridge and is to be distinguished from the dorsal ventricular ridge which is derived from the general pallium and corresponds to the caudate nucleus.

24. The folding in reptiles, besides crowding the central nucleus into its deep position, gave rise to a new nucleus, the basal nucleus amygdalæ. This nucleus is large celled in turtles but in the opossum and mammals it consists of large-celled and small-celled parts.

25. In marsupials and mammals the continued hypertrophy at the fissura amygdalæ and in-wandering of cells gave rise to the large lateral nucleus which took up a position in the lateral wall of the ventricle internal to the external capsule.

26. While the basal nucleus receives important fiber bundles of the stria terminalis it is more closely related to the pyriform cortex than are the older parts of the amygdala. The lateral nucleus has little connection with the stria terminalis but has its fiber connections chiefly with the pyriform cortex, the putamen and the diagonal band system.

27. A longitudinal bundle appearing first in the marsupials as an association bundle between parts of the amygdala and the pyriform cortex and as a pathway connecting these centers with other centers by way of the diagonal band becomes more important in higher forms and is one of the chief fiber paths for the newer (basal and lateral) amygdaloid nuclei. This is the 'sagittales Längsbundel' of earlier authors.

28. The diffuse bundles of fibers here referred to which lead out of the amygdala below the anterior commissure and in the deepest part of the diagonal band enter the region of the medial forebrain bundle and may descend in it to lower centers.

29. Among these diffuse fibers are some small bundles (z) which run from the amygdala to the tuberculum olfactorium.

30. Another fiber system in human foetuses (y) comes out of the pyriform lobe as distinct bundles near the temporal limb of the anterior commissure. These run in the direction of the precommissural system but become diffuse and are lost. They may arise from the pyriform cortex or from the amygdala.

31. Another system in the human foetus (x) coming from the same region follows the anterior commissure for some distance then breaks through the diagonal band as diffuse fascicles which join the medial forebrain bundle descending toward the hypothalamus.

All these fiber systems require further study.

32. The amygdaloid complex of reptiles and mammals is derived from the caudal part of the lateral olfactory area and of the basal area of the selachian brain. While this part of the olfactory area may have been concerned in part with gustatory impressions, its position in immediate contact with the somatic correlation centers determined that the correlation of olfactory with somatic impressions should be the chief influence directing the development of the amygdaloid complex.

33. The pyriform cortex adjacent to the general pallium became most directly involved in olfacto-somatic correlation. When vertebrates came to live on land the tremendously increased number, range and variety of stimuli led not only to the great expansion of the general pallium but also to an increase in the centers for correlation of olfactory with somatic impressions. This was the occasion for the formation of the new nuclei out of the pyriform lobe in the manner above described.

LITERATURE CITED

CAJAL, S. RAMÓN 1904 Textura del sistema nervioso del hombre y de los vertebrados, vol. 2.

CROSBY, ELIZABETH C. 1917 The forebrain of Alligator mississippiensis. Jour. Comp. Neur., vol. 27.

DE LANGE, S. J. 1911 Das Vorderhirn der Reptilien. Folia Neurobiologica, Bd. 5.

EDINGER, L. 1896 Vorlesungen u. s. w.

HERRICK, C. JUDSON 1905 The central gustatory paths in the brains of bony fishes. Jour. Comp. Neur., vol. 15.

1910 The morphology of the forebrain in Amphibia and Reptilia. Jour. Comp. Neur., vol. 20.

1921 a A sketch of the origin of the cerebral hemispheres. Jour. Comp. Neur., vol. 32.

1921 b The connections of the vomero-nasal nerve, accessory olfactory bulb and amygdala in Amphibia. Jour. Comp. Neur., vol. 33.

HERRICK, C. L. 1891 Histology of the rhinencephalon and prosencephalon. Jour. Comp. Neur., vol. 1.

1893 Topography and histology of the brain of certain reptiles. Jour. Comp. Neur., vol. 3.

HINES, MARION 1922 Studies in the growth and differentiation of the telencephalon in man. The fissura hippocampi. Jour. Comp. Neur., vol. 34.

HOLMGREN, NILS 1922 Points of view concerning forebrain morphology in lower vertebrates. Jour. Comp. Neur., vol. 34.

HUNT, J. RAMSAY 1917 Progressive atrophy of the globus pallidus. Brain, vol. 40.

JOHNSTON, J. B. 1906 Nervous system of vertebrates. Philadelphia: Blakiston.

1909 a The central nervous system of vertebrates, Ergebn. u. Fortschr. der Zoologie, Bd. 2.

1909 b The morphology of the forebrain vesicle in vertebrates. Jour. Comp. Neur. Psych., vol. 19.

1910 b The problem of the correlation mechanisms. Anat. Rec., vol. 4.

1910 c The evolution of the cerebral cortex. Anat. Rec., vol. 4.

1911 a The telencephalon of selachians. Jour. Comp. Neur., vol. 21.

1911 b The telencephalon of ganoids and teleosts. Jour. Comp. Neur., vol. 21.

Johnston, J. B. 1912 b The telencephalon in cyclostomes. Jour. Comp. Neur., vol. 23.

1913 b The morphology of the septum, hippocampus, and pallial commissures in reptiles and mammals. Jour. Comp. Neur., vol. 23.

1915 b The cell masses in the forebrain of the turtle, Cistudo carolina. Jour. Comp. Neur., vol. 25.

1916 a Evidence of a motor pallium in the forebrain of reptiles. Jour. Comp. Neur., vol. 26.

1916 b The development of the dorsal ventricular ridge in turtles. Jour. Comp. Neur., vol. 26.

1918. The history of the nucleus caudatus and the stria terminalis in vertebrates. Anat. Rec., vol. 14.

Kappers, C. U. Ariens 1908 Die Phylogenese des Rhincencephalons, des Corpus striatum und der Vorderhirnkommissuren. Folia Neurobiol., Bd. 1.

Kölliker, A. 1896 Gewebelehre. 6 Aufl. Bd. 2. Engelmann.

Meyer, A. 1892 Ueber das Vorderhirn einiger Reptilien. Zeit. wiss. Zool., Bd. 55.

Shellshear, Joseph L. 1920. The basal arteries of the forebrain and their functional significance. Jour. of Anat., vol. 55.

Smith, G. Elliott 1902 Catalogue of physiol. series of comp. anat. museum of Royal Coll. of Surgeons of England, vol. 2, 2nd edition.

1908 The cerebral cortex in Lepidosiren, Anat. Anzeiger, Bd. 33.

1910 The Arris and Gale Lectures. The Lancet, Jan. 1, 15, and 22.

1919 A preliminary note on the morphology of the corpus striatum and the origin of the neopallium. Jour. of Anat., vol. 53.

Söderberg, Gertie 1922 Contributions to the forebrain morphology in Amphibians. Acta Zoologia. Bd. 3. 1922.

Völsch, Max 1906 Zur vergleichenden Anatomie des Mandelkerns und seiner Nachbargebilde. I. Arch. f. mikr. Anat., Bd. 68.

1910 The same, II. Arch. f. mikr. Anat., Bd. 76.

Wilson, S. A. Kinnier 1914 An experimental research into the anatomy and physiology of the corpus striatum. Brain vol. 36.

Ziehen, Th. 1901 Das Zentralnervensystem der Monotremen und Marsupialier, I. II. Denkschriften der Medizinischnaturwissenschaftlichen Gesellschaft zu Jena, Bd. 6.

L-612

AUTHOR'S ABSTRACT OF THIS PAPER ISSUED BY THE BIBLIOGRAPHIC SERVICE, NOVEMBER 26

Reprinted from THE JOURNAL OF COMPARATIVE NEUROLOGY, Vol. 36, No. 2, December, 1923.

FURTHER CONTRIBUTIONS TO THE STUDY OF THE EVOLUTION OF THE FOREBRAIN

V. SURVEY OF FOREBRAIN MORPHOLOGY

J. B. JOHNSTON

Anatomical Laboratory, University of Minnesota

THIRTY-TWO FIGURES

In this section references are made to the description and figures contained in sections I to IV published in this Journal for August, 1923.

A. GENERAL CONSIDERATIONS

In preparation for the discussion of the evolution of the forebrain some reference must be made to the results of studies by many workers during fifty years upon the evolution and morphology of the vertebrate head. The process of cephalization has consisted largely of modifications in the anterior segments due to the location of mouth and special sense organs in that region. There have been modifications in the trunk as well as in the head. No segment in existing vertebrates presents unmodified the structures of a typical or primitive segment. Any discussion of the problem of cephalization must take into account all the elements which enter into a complete segment and in particular must give consideration to all four functional divisions of the nervous system. Notable modifications of the segments in the occipito-spinal and branchial regions need not be considered here since they do not directly affect the evolution of the forebrain.

1. In the ontogeny of the nervous system two broad stages are recognized: that of the neural plate and that of the neural tube. Between these occurs a transitional period during which the neural tube presents an open anterior neuropore. It is clear that the neural plate represents a ring of nervous ectoderm which

surrounds the primitive blastopore and it is probable that the period of the open neuropore represents the last part of the gastrula stage of evolution during which the neurenteric canal served for the ingestion of food. If so, the closing of the neuropore must have taken place after the formation of a direct opening to the enteric cavity (palaeostoma). On this hypothesis it would be assumed that the closed neural tube has existed during all the time necessary for the evolution of the enteric cavity, the development of the branchial apparatus, the formation of the mouth with jaws, etc.

2. During the neural plate and open neuropore stages there was established a front end or foremost border of the central nervous system. It has been shown that this anterior end is marked by the optic chiasma of the adult brain of all vertebrates (terminal ridge in the embryonic brain; Johnston, '09 b). This has been confirmed by Kingsbury ('20, '22).

All parts of the diencephalon and telencephalon including the cerebral hemispheres must be regarded as derivatives of the walls of the neural tube morphologically caudal to the chiasma ridge.

3. The whole diencephalic and telencephalic region is lacking in effective nerves or centers and this fact has offered serious difficulty to all attempts to compare the divisions of this region to the segments of the head and trunk caudal to the level of the oculomotor nerve. There has been great difficulty also in all attempts to trace forward the equivalents of the two columns of His (sensory alar plates and motor basal plates) into the diencephalon and telencephalon. The floor of these brain segments instead of resembling the motor basal plates is made up chiefly of centers related to the olfactory and gustatory systems. If the statement of His that the sulcus limitans, marking the boundary between sensory alar and motor basal plates, ends in the preoptic recess be accepted, the conclusion must follow that the floor of the diencephalon belongs to the motor plates. In many studies between 1901 and 1913 the writer struggled to harmonize this assumption with the obvious relationship of the whole hypothalamic region with sensory systems (olfactory and gustatory). The only conclusion arrived at was that motor elements have

evidently disappeared and that the centers of this region are to be compared with tract and commissural cells having associational functions at all levels of the neural axis. This conflict is now resolved by the introduction of a new point of view by Kingsbury (see below).

Anterior to the myotome supplied by the oculomotor nerve (premandibular somite) there exist in embryos transient structures supposed to represent muscles once existing in this region of which we have no knowledge. These structures are the anterior head cavities and the median mesoderm connecting them in selachian embryos, and the corresponding median mesoderm plate in vertebrate embryos generally, known as the prechordal plate.

The lack of muscle segments and of motor nerves and centers places this anterior region in sharp contrast to the clearly recognized head and trunk segments. We have here only a portion of the brain together with special sense organs, skeletal, vascular, and other subsidiary tissues. This region Neal includes in the first head segment.

4. A very important factor in the interpretation of the anterior part of the neural tube is found in the extent of the floor plate of His. This is brought forward by Kingsbury in two very illuminating discussions ('20, '22). The floor plate of His is the median seam connecting the two basal plates. This seam is marked in neural plate stages of embryos by the primitive streak which owes its origin to the closing of the blastopore. Everyone who has studied these stages has noticed that the primitive streak does not extend throughout the whole length of the neural plate but stops some distance behind the anterior end. In later embryos and adults there is a median seam in the floor of spinal cord and hind-brain in which there is a strongly developed system of fibers derived from the ependyma cells along the median plane. This peculiar structure is known to neurologists as the raphé. This raphé does not extend through the whole neural tube but is absent at least in the telencephalon and diencephalon.

Professor Kingsbury, treating these facts from the standpoint of the blastopore theory, shows that the raphé is coextensive with the closed-up blastopore or neurochordal seam and plate, and that it is important to distinguish that part of the brain which does not possess a true raphé (prechordal brain) from that which does (epichordal brain). The point of view presented by Kingsbury leads to the solution of many perplexing problems connected with the fundamental morphology of the diencephalon and telencephalon.

First of all it is very clear that the region of the prechordal brain cannot be divided into segments which, taken with sense organs and transient or persistent nerve- and muscle-elements, may be described as head segments. The writer abandons his earlier recognition of two or more head segments in this region and accepts, in general terms, the views of Neal ('98, '14, '18, '19) as to brain segmentation.

The myotomes are derived from the primitive streak (lips of the blastopore) and are approximately coextensive with the primitive streak. The anterior and premandibular head cavities are joined with their fellows across the median plane by the prechordal plate. This median plate may be regarded as a remnant of the mesoderm primitively confluent in front of the blastopore. We do not know whether the anterior head cavities represent vestiges of once existing muscle masses. What is clear is that the region anterior to the myotome supplied by the oculomotor nerve has not been shown to possess these essential elements of a true head segment: *a*) myotomes which develop muscles in at least some existing vertebrates, *b*) somatic effective nerve components and nuclei of origin in the brain, *c*) visceral effective nerve components arising from this part of the brain.

There is no definite evidence that these structures ever existed and have aborted. In the absence of these structures it is impossible to speak of head segments. The suggestion is offered that the region represented by the first brain segment of Neal is in reality a pre-metameric region. This pre-metameric region contains the forebrain, paired eyes and olfactory organs, the pineal eye, palaeostoma, hypophysis, infundibulum, and prechordal mesoderm. In all the rest of the head and body the metamerism is complete; that is, each metamere includes somatic and visceral effective nervous mechanisms and muscles as well as sensory systems and correlating nerve centers.

Adelmann ('22) from a study of the prechordal plate in selachians and the chick comes to the conclusion, "If, then, as I have shown, the mesoderm is continuous around the anterior end of the notochord and the premandibular somites are formed by the lateral growth of a single, medial pre-axial mesodermal mass, it follows that we have to do here with a line of somites which is continuous around the anterior end of the notochord."

This contribution of Kingsbury's has introduced a new and quite fundamental factor into our conception of the nature of the forebrain which must serve as the starting point in a study of its evolution in the vertebrate series. The earlier view, that the forebrain represents one or more typical metameres which once existed at least in vertebrate ancestors, and that these metameres have lost their effective systems (muscles, nerves, motor centers), implied that the forebrain is a continuation of the neural tube in which the effective centers have atrophied because the peripheral organs have been lost. On the other hand, special sense organs and correlating centers have had a special development, which accounts for great peculiarities of form and such neomorphs as the cerebral hemispheres.

Kingsbury brings forward evidence that what is here called the premetameric neural tube is fundamentally devoid of effective mechanisms, that the basal plates of His do not continue forward into this region, that the sulcus limitans does not extend into it, and that the floor of the neural tube in this region is formed by the alar plates of the two sides which are continuous across the median plane. This may be expressed by saying that the nervous ectoderm, like the mesoderm, surrounded the blastopore, and the pre-metameric brain represents that part of the neural plate which encircled the blastopore in front.

The results of Kingsbury's observations do not mean that the anterior end of the nervous system was at the anterior end of the primitive streak, but that the streak (or neurochordal seam) marks the extent of the typical metameric portion of the nervous system. In front of this is a central nervous region without a true raphé and devoid of effective mechanisms, but consisting of certain special sensory mechanisms and of correlating centers to which impulses come from the metameres and from which directive impulses are sent to the metameres.

The neural plate in the ontogeny represents an area of ectoderm of high sensitivity which primitively surrounded the gastrula mouth or blastopore. That part which lay at the sides of the blastopore after its elongation came to be divided into segments corresponding to the myomeres, the anterior part remained undivided as a pre-metameric region or head segment. In the metameric part the nervous ectoderm came to be differentiated into longitudinal columns each of which contained the centers for one of the functional divisions of the nervous system: somatic receptive, visceral receptive, visceral effective, somatic effective (Johnston, '02 c). The arrangement of these in the neural plate is illustrated in figure 1 and in '02 c, '06, '09 a. In each half of the neural plate the four columns lay in the order above named, beginning with the lateral border. No superficial indication of the dividing lines between these columns is seen on the open neural plate but when the plate rolls up into a tube there

ABBREVIATIONS

a. b., area basalis
a. o. l., area olfactoria lateralis
b. o., bulbus olfactorius
cbl., cerebellum
ch., optic chiasma
c. p., commissura posterior
c. p. p., commissura pallii posterior
fov., fovea isthmi
g. p., general pallium
h., hippocampal formation
hab., nucleus habenulae
hem., cerebral hemisphere
hy., hypophysis
hyth., hypothalamus
l. s., lamina supraneuroporica
l. t., lamina terminalis
m., mouth
man., mandibular arch
nch., notochord
n. l., nucleus lentiformis
op. v., optic vesicle
r. i., recessus infundibuli
r. m., recessus mamillaris
r. n., recessus neuroporicus
r. p., recessus preopticus
r. po., recessus postopticus
s. l. H., sulcus limitans of His
s. m., somatic motor or effective column
s. s., somatic sensory or receptive column
ter., terminal ridge
t. p., tuberculum posterius
v. m., visceral motor or effective column
v. s., visceral sensory or receptive column
v. t. o., ventricle of the tuberculum olfactorium
z. l. m., zona limitans medialis
III, nervus oculomotorius
IV, nervus trochlearis

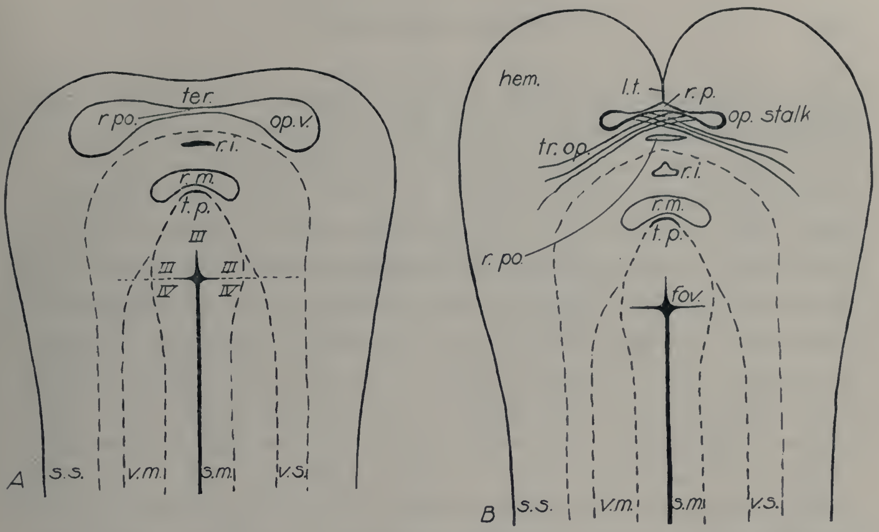


Fig. 1 Two diagrams of the arrangements of the functional columns in the anterior portion of the neural plate and tube. Based on the work of Kingsbury and the discussion in the present paper.

In A, showing the open neural plate, the floor plate is represented by a heavy line ending forward in something like a spearhead indicating the fovea isthmi and the transverse grooves running from it in the lateral walls of the midbrain. About the fovea are grouped the nuclei of the III and IV nerves in agreement with Kingsbury's figure 6 ('20). The functional columns are outlined by broken lines: *s.s.*, somatic sensory; *v.s.*, visceral sensory; *v.m.*, visceral motor; *s.m.*, somatic motor. The sulcus limitans of His, lateral to *v.m.* does not extend forward beyond the mammillary recess. The anterior end of the motor basal laminae is marked by the tuberculum posterius. The mammillary recess and infundibular recess lie in the region where the visceral sensory laminae are confluent across the middle line. The pits which evaginate to form the optic vesicles are located within the somatic sensory laminae and are connected with one another across the midline by the primitive optic groove which later becomes the postoptic recess (*r.po.*). The primitive optic groove is bounded in front by the terminal ridge (*ter.*) which is the neural ridge bounding the neural plate and forms the anterior border of the plate in the midline.

In B the neural plate is supposed to have rolled up into a tube which is represented as laid open along the dorsal seam. The relationships are the same as in *A* except that the region of the future hemispheres (*hem.*) has expanded forward and the terminal ridge has been converted into the optic chiasma, indicated by the crossing fibers of the optic tracts. The lamina terminalis is the anterior end of the dorsal seam which meets the anterior end of the brain floor (not floor plate) at the terminal ridge. Fibers from the retinas entering the brain along the optic stalks cross in the terminal ridge forming the optic chiasma. The optic tracts occupy an oblique thickening in the brain wall leading from the terminal ridge toward the thalamus. This optic ridge cuts off the optic stalk from the primitive optic groove. The optic stalks then appear to be connected with one another at the lower border of the lamina terminalis. The pit or recess formed here is known as the recessus preopticus (*r.p.*), while the primitive optic groove behind the terminal ridge remains as the recessus postopticus (*r.po.*).

appears on the inner wall of the tube on each side the sulcus limitans of His, who recognized that this groove marked the line of division between the effective and receptive columns.

His regarded the neural tube as a tube whose roof plate and floor plate were of equal length and whose anterior end was closed by a terminal plate (lamina terminalis). The writer has shown ('09 b) that the lamina terminalis must be regarded as the anterior portion of the roof plate, while Kingsbury ('20, '22) has shown that the anterior part of the brain floor does not possess a floor plate in the sense of a seam connecting the two basal plates of His. Since all these facts go to show that the pre-metameric brain is a highly special region, differing in very important respects from the metameric brain, it becomes of the greatest interest to determine the line of demarcation between the two. Evidences upon this point are found in, *a*) the extent of the raphé in the brain, *b*) the relations of the notochord and brain in embryos, *c*) the structure of the brain walls, and *d*) the extent of the sulcus limitans of His in the embryonic brain.

Kingsbury states that the raphé stops anteriorly at the fovea isthmi and that the anterior end of the notochord in the embryo seems to him to lie at about the same level. He therefore regards the fovea isthmi as the mark of the anterior end of the epichordal brain.

I would point out that the characteristics of the floor plate seem to extend forward somewhat beyond the fovea and that the region between the fovea and the tuberculum posterius possesses peculiarities of structure which distinguish it from the mammillary, infundibular, and chiasmatic regions. In embryos of Acanthias, Amia, pigeon, pig, sheep and man there is found not a sudden stopping of raphé fibers at the fovea but a rapid change to a condition in which the ependyma fibers are more sparse and are separated by large numbers of infiltrated cells (figs. 22 and 24).

In Amblystoma embryos at the stage when the mammillary recess becomes recognizable as a ventro-caudal pouch with a thin wall of flattened cells there is a remarkably clear differentiation of the brain floor in the median plane caudal to this recess. Beginning behind the tuberculum posterius the floor in the median plane consists of a continuous layer of high columnar cells which are heavily pigmented on their internal ends (fig. 30), while no comparable pigmentation is found elsewhere in the neural tube at this stage. This condition continues almost without interruption right back through the length of the spinal cord. These columnar pigmented cells form only a narrow streak at the median plane. These cells undoubtedly constitute the floor plate in the sense of His and Kingsbury in the spinal cord and hind-brain. I find it difficult to believe that those in front of the fovea do not belong to the floor plate also. These pigmented columnar cells are probably the cells which later give rise to the ependyma cells and raphé fibers.

In Acanthias of 14 mm. the brain floor in the median plane consists of one layer of columnar cells up to a point near the mammillary recess, while the mammillary, infundibular, and optic chiasma regions are filled with neuroblasts many of which are pear-shaped and show the axone process. The brain floor in front of the tuberculum posterius seems to be constituted chiefly of neuroblasts in all the embryos studied.

5. The question of the relation of the anterior end of the notochord to the brain is very difficult, as Dr. Kingsbury recognizes. The extent of the notochord itself is uncertain, since it frequently blends with the prechordal mesoderm. The unequal growth of the brain producing sharp flexures moves the parts with reference to one another in successive stages of development.

Embryos of Amblystoma illustrate in a striking way the shifting of position of the anterior end of the notochord with reference to the parts of the brain. In embryos of about the stage shown in figure 29 the notochord ends beneath the medulla oblongata far behind the cerebellum. Numerous older embryos, one of which is shown in figure 32, have the notochord in contact with the hypophysis and floor of the diencephalon, as a result of the brain flexure, although the end of the notochord still lies beneath the medulla oblongata. But now, early embryos in which the brain flexure merely follows the curvature of the egg (fig. 28) show the notochord following the same curvature and ending relatively far forward in contact with a thickening of the brain floor. This thickening contains a median sagittal cleft which is a ventro-caudal keel-like prolongation of the forebrain ventricle. This thickening with its ventricle represents the early downgrowth of the infundibular and mammillary regions. The thick walls contain many more mitotic figures than are found elsewhere in the brain walls at this stage. By the time those structures have clearly differentiated, the growth of brain, myotomes and enteron have pushed the forebrain vesicle forward far from the end of the notochord, as shown in figure 29. In these early stages the end of the notochord lies close behind the mammillary recess.

6. The structure of the brain wall interests us here because of the presence of the nucleus and root of the oculomotor nerve rostral to the fovea isthmi. In Acanthias, Amia, Acipenser, Polyodon, Amblystoma, Necturus, Chelydra, and in human embryos the fovea is found just caudal to the third nerve. Neal ('19, figs. 7, 8) shows the fovea separating the nuclei of the third and fourth nerves. He says, "The lateral recess in the floor of the brain lies within the limits of the midbrain vesicle and does not indicate a boundary between the primary brain divisions." Herrick ('21, fig. 65) has indicated that it lies between the third and fourth nerves in Necturus. In Acanthias, Amia, Amblystoma (fig. 32) and Chelydra the fovea is continued by a sulcus in the lateral wall which leads up into the caudal part of the tectum mesencephali. Whether the fovea and sulcus isthmi are considered as internal marks of the isthmus (Herrick) or are assigned to the mesencephalon (Neal) as their position seems to indicate, need not be discussed here. At least the greater part of the base of the midbrain including the nuclei of the third nerve lies in front of the fovea. Kingsbury clearly regards this as a region in which the basal plates of His are confluent in front of the blastopore, and notices the location here of a nucleus centralis nervi oculomotorii and other median nuclei and the existence of crossed origins of oculomotor root fibers as evidence of continuity between the two lateral halves. In accordance with this the midbrain must be regarded as part of the prechordal brain and the oculomotor nerves with the premandibular myotomes must be assigned

to that preaxial common mass in front of the concrescence area which Kingsbury clearly recognized, but which His, Hertwig and Minot only vaguely appreciated. This means that the first segment of Neal contains the forebrain vesicle, eyes, olfactory organs, palaeostoma, infundibulum-hypophysis, and prechordal mesoderm but no muscles; the second segment contains midbrain, premandibular myotomes and their motor nerves (III), the ophthalmicus profundus nerve but no branchial element; the third and following segments present the essential elements of complete axial metameres. The axis of these metameres is marked by the notochord and floor plate of the neural tube, or by the neurochordal suture.

7. The forward extent of the sulcus limitans of His which separates the sensory and motor columns in the lateral walls of the brain tube is of importance in this connection. His traced this forward to the preoptic recess. Kingsbury states with apparent approval that Schulte and Tilney ('15) have shown that the sulcus limitans in cat embryos cannot be traced farther forward than the midbrain. In my earlier work I adhered to the view of His that this sulcus ended in the preoptic recess. In 1912, however, in connection with the study of ventricular sulci in the diencephalon and telencephalon of cyclostomes it became clear that the sulcus limitans does not continue forward beyond its junction with the hypothalamic sulcus ('12 b, p. 347, and figs. 5 and 6). This led me to a study of the sulcus limitans of His in a wide range of comparative material. From the study of a large number of forms I came to the conclusion that the recognition of a sulcus limitans ending in the preoptic recess is based on the assumption that the groove which is observed ending in the preoptic recess is traceable through the midbrain and cerebellum to the undoubted sulcus limitans in the medulla oblongata. I was unable to trace the continuity of these sulci. I have recently reviewed the same material and studied other materials and am quite unable to find any clear evidence that the sulcus in the hindbrain and cord regions which is undoubtedly the sulcus limitans of His continues farther forward than the mammillary recess in any form studied.

In the brains of adult fishes the sulcus limitans of His is very clearly identified in the medulla oblongata. It forms the immediate ventral boundary of the vagal and facial lobes and is perfectly evident as far forward as the sensory root of the VII nerve. In Squalus acanthias and Scyllium the sulcus limitans is lost behind the cerebellum. A little lateral to it appears a deeper groove which marks the angle between the cerebellum and lateral wall. If this be considered the continuation of the sulcus limitans, it becomes broad and shallow and disappears at the level of the III nerve. A little farther forward the groove seems to reappear and goes up above the ridge containing the fibers of the posterior commissure to end in the tectum mesencephali.

In young embryos of Squalus and Scyllium (from 2.5 to 8.4 mm.) there is no sulcus limitans recognizable. In Squalus of 20.5 mm. a prominent groove in the medulla oblongata which one might suppose was the sulcus limitans runs forward to end in the dorsal wall of the cerebellum, behind the isthmus. In Squalus of 33.1 mm. (fig. 23) a small groove is clearly seen at the level of the VII and V nerves separating the sensory and motor nuclei of those nerves. This answers to the definition of the sulcus limitans. It is indistinct between the VII and V nerves and disappears a short distance forward from the V nerve. Two much more prominent grooves are seen in this region, one dorsal to the sensory nuclei of VII and V and one ventral to the motor nuclei of these nerves. Obviously neither of these is the sulcus limitans, but it would be easy for one who did not give careful consideration to their relations to the nerve roots and nuclei, to mistake one of those grooves for the sulcus limitans.

In adult Acipenser the sulcus limitans is lost at the root of VII. At the V nerve a new groove appears which goes up behind the posterior commissure as in selachians. In adult Amia the conditions are about the same. In Amia of 11 mm. and 25 mm. the sulcus limitans is lost in the auricular lobes of the cerebellum. The groove which may be considered to represent it farther forward stops behind the fovea isthmi. In Lepidosteus of 25 mm. likewise the sulcus can be followed forward past the V nerve but ends in the auricular lobe of the cerebellum. Although in these young ganoids a small sharp ependymal groove runs back from the preoptic recess, which can be followed either as a groove or thickening of ependyma to the isthmus (Johnston, '11 b, p. 522), behind the isthmus this groove enters the dorsal part of the cerebellar ventricle and does not meet the sulcus limitans. Moreover, after seeing the complexity of ventricular grooves present in the diencephalon and mesencephalon, I would not be willing to say that this slender ependymal groove throughout this whole distance should be regarded as an entity distinct from the other grooves which it crosses between the preoptic recess and the isthmus. In Ameiurus of 25 mm. the sulcus limitans merges with the groove between cerebellum and lateral wall, rises to the dorsal part of the ventricle and disappears beneath the cerebellum.

In older stages of Amblystoma larvae what appears to be the sulcus limitans of the medulla oblongata enters the auricular lobe of the cerebellum. In earlier stages it is clear that the sulcus is continued through the cerebellum. This continuation groove in all stages descends in the lateral wall and ends at the side of the fovea isthmi. The two grooves give to the section of the ventricle the form of an inverted Y, between the arms of which lies the fovea, or the three are merged into a broad rounded fovea.

In embryos of Chelydra serpentina of 8½ mm. carapace the sulcus which seems to represent the sulcus limitans in the cerebellar segment runs forward into the mammillary recess.

Human embryos of the following stages have been studied: C. R. length 9, 11, 13, 18, 19, 20, 21, 22, 24, 25 mm. The embryos of 9, 11, and 13 mm. are cut in such a plane that the course of the sulcus limitans can be studied only in models. The 9 mm. embryo was received in a perfectly fresh condition and was admirably fixed, cut in a faultless series and well stained. Of this brain I possess a model made by an assistant years ago for an entirely different purpose and before this question came up for consideration. It is an excellent piece of workmanship and shows the grooves and ridges on the internal surface of the brain very clearly. The sulcus limitans has a somewhat zig-zag course across the transverse 'neuromeric' grooves in the wall of the medulla oblongata. I should be somewhat doubtful whether the groove which passes forward through the cerebellum and midbrain is really a continuation of the sulcus limitans. Granted that it is, this groove comes into close relation with the mammillary recess. From the mammillary recess a groove extends forward to meet the groove which rises from the preoptic recess to the interventricular forearm. While this model might bear the usual interpretation, I do not think that it would lead anyone to conclude that the sulcus limitans extends to the preoptic recess, unless the observer were influenced by a preconception based on the description of His. It is clear, however, that the longitudinal sulcus found in the cerebellar segment extends through the midbrain as far as the mammillary recess.

In the older embryos mentioned the sulcus limitans crosses the deepest of the neuromeric grooves at the level of the pontile flexure and then bends dorsad to end in the roof of the cerebellum behind the decussation of the IV nerve. In other words, the sulcus limitans merges with the transverse groove of the cerebellar neuromere and is lost.

So far as independent evidence from the sulcus limitans is concerned, then, the materials at my disposal do not make clear that it can be traced forward with certainty beyond the level of the trigeminus. There is a serious question whether the sulcus limitans has been properly identified in all studies of this subject. A sharply marked sulcus in the cerebellum and forward is not often present in young embryos. There is a tendency for the sulcus limitans to merge with one of the transverse grooves and then it has the appearance of ending in the roof (Squalus, Ameiurus, man) or the floor (Amblystoma). The utmost forward extent which the writer could admit on the basis of his material would be the mammillary recess (Chelydra and 9 mm. human embryos). The existence of sensory and motor centers in the midbrain comparable with those of the medulla oblongata and spinal cord would lead us to expect that a sulcus limitans would be found in the midbrain.

8. The writer is inclined to believe that all the facts at present known are best explained by regarding the region of the midbrain, oculomotor nerves, and premandibular myotomes as a transi-

tional region between the pre-metameric region (Neal's segment I) and the true metameric region beginning with the segment of the cerebellum and mandibular myotome and arch (Neal's segment III). In this second, transitional segment some of the elements of a complete metamere are lacking. The midbrain floor includes the nuclei of the most anterior pair of motor nerves and is traversed for a part of its length by the neurochordal suture. This is represented by the fovea isthmi and by columnar floor plate cells in the young embryos and raphé fibers in older stages continuing forward in the rostral wall of the fovea. Thus the midbrain segment includes the extreme anterior angle of the fused blastopore lips and also the confluent basal plates of the neural tube and confluent prechordal plate of the mesoderm, these being formed from the neural ectoderm and the entoderm which encircled the blastopore in front. At or near the tuberculum posterius occurs a sharp transition in the structure of the brain floor which marks the boundary between basal plates and alar plates of His. This is further evidenced by the convergence of the sulcus limitans of His, in the forms in which it is most fully preserved, at the mammillary region. The alar plates of His therefore give rise to the larger dorsal portion of the midbrain and the entire forebrain (diencephalon and telencephalon). Along with this exclusively sensory forebrain there entered into the premetameric region a non-muscle-forming mass of mesoderm including the prechordal plate and the anterior head cavities of selachians and the narrow preoral entoderm which served for the primitive connection of the enteron with the ectoderm (palaeostoma).

These conclusions are in essential agreement with the results of Neal on head segmentation which he has concisely summarized in his 1914 paper. In a later paper ('18) Neal has brought together reasons for considering the eye-muscle segments as members of a continuous series of metameres in the vertebrate body. My conclusions are also in agreement with Kingsbury in all important respects.

For the purpose of studying the evolution of the cerebral hemispheres, the general result of this survey of head segmentation of importance to us is that the embryonic forebrain vesicle from which the telencephalon and diencephalon are derived is itself formed from a part of the neural plate which originally lay anterior to the cephalic end of the neurochordal seam (primitive blastopore) and consisted of nervous ectodermal tissue comparable to the sensory alar plates of His. Whether the supposition that the midbrain with the premandibular myotomes and the III nerves is penetrated by the cephalic end of the neurochordal seam is correct or not is immaterial to the further consideration of the forebrain.[1]

---

[1] In a recent study of Amblystoma embryos Burr ('22) has come to the conclusion that: "Between the fovea isthmi and the preoptic recess the midventral portion of the neural plate is occupied by the continuity of the lateral basal laminae. Between the preoptic recess and the lamina terminalis the mid-ventral portion of the neural plate is occupied by the terminal ridge, the continuity of the lateral alar plates."

It is necessary to correct the following statement of results attributed to the present writer: "The work of Johnston ('09), based on a comparative study of the forebrain vesicle in vertebrates, showed clearly that the ventral lip of the neuropore was incorporated into the brain as the terminal ridge lying between the lamina terminalis anteriorly and the chiasmatic ridge posteriorly through the fusion of the lateral lip of the blastopore (sic., neuropore intended ?). He concluded that the preoptic recess, marking the termination of the sulcus limitans and separating the terminal ridge from the chiasmatic ridge, represented the meeting-point of the roof and floor plate and hence the anterior end of the neural tube" (Burr, p. 278). In the paper referred to the writer stated: "After the brain is separated from the ectoderm the terminal ridge forms a distinct fold convex toward the ventricle, which in later stages is occupied by the fibers of the optic tracts in the chiasma" (p. 491; also p. 481). "The anterior boundary of the neural plate is formed by a transverse ridge, the terminal ridge which is continuous with the neural folds bounding the neural plate laterally. This terminal ridge is clearly seen in successive stages and is readily followed up to the time when the optic chiasma is formed in it" (p. 504). "Early stages show clearly that the basal axis of the brain ends not in the Basilarleiste but in the terminal ridge in which later the optic chiasma appears" (p. 506). "The optic chiasma is formed in the terminal ridge and therefore occupies the anterior border of the brain floor" (p. 532).

The terminal ridge does not lie between the lamina terminalis and the chiasmatic ridge, but is the chiasmatic ridge. The terminal ridge is not formed through the fusion of the lips of the neuropore but is the persistent neural ridge which bounds the neural plate anteriorly. The preoptic recess cannot separate the terminal ridge and chiasmatic ridge which are one and the same thing. The body which Burr figures as the terminal ridge is only a transitory mass of neural ridge cells caused by the coming together of the lips of the neuropore. It later thins out and forms part of the lamina terminalis. The preoptic recess is formed by thinning of the lower part of this adjacent to the true terminal or chiasmatic ridge. My statements on these points were quite clear and explicit and they have been correctly understood and

9. The neural plate anterior to the primitive streak consisted of unsegmented ectoderm which primitively surrounded the anterior border of the blastopore. Throughout the head region the boundary of the neural plate was at first probably indistinct or irregular. Not only are nerve ganglia separated off from its border during the ontogeny, but such structures as the acusticolateral placodes, the visceral ganglion placodes, and the olfactory placode were formed from ectoderm more or less closely associated with the border of the neural plate. The recent description by Stone ('22) of the general cutaneous components of the cranial nerves in Amblystoma arising from ectodermal placodes further emphasizes the conception of the neural ectoderm as a broad irregular and undefined area only a part, and probably a variable part, of which enters into the neural plate and rolls up into a neural tube. The anterior boundary of this neural plate in the ontogeny is formed by the confluence of the neural ridge in the terminal ridge and this terminal ridge comes to be occupied by

---

quoted by Kingsbury ('20, '22). Burr's further statement that, "In any event, it seems evident that this terminal ridge is subsequently occupied by decussating fibers of the anterior commissure" is erroneous. His so-called terminal ridge disappears and the bed of the anterior commissure is formed by a new thickening of the lamina terminalis formed by invasion from the striatal ridges.

Burr tried by experiment to determine the fate of the lower border of the neuropore. His Nile-blue sulphate experiment, however, was begun much too late for this purpose. The neuropore was already drawing together and the transitory plate which he calls terminal ridge had already been formed before the experiment was begun. The Nile-blue sulphate would need to be applied to the terminal ridge in the open neural plate stages. Burr states (p. 283) that, "The fundamental arrangements of the longitudinal columns of His in the rostral end of the neural tube were as indicated by Kingsbury ('20) in his figure 6," but differs from Kingsbury in assigning the optic chiasma and hypothalamus to the basal plates. Kingsbury ('20, pp. 128–129) says, "It is in my opinion a valid objection to the generally accepted interpretation that it includes in the basal, primary motor lamina optic chiasma and hypothalamus —regions which possess no such significance. The motor zone ceases with the floor of the midbrain. . . . The telencephalon and diencephalon would then be entirely developed out of alar-plate material." In his second paper Kingsbury ('22) states that the boundary between basilar and alar plates clearly lies in the region of the mammillary recess.

With regard to the first of the two conclusions above quoted, the whole preceding discussion is opposed to the view that the hypothalamus and optic chiasma are derived from the basal laminae of His. With regard to the second conclusion, the space between the preoptic recess and the lamina terminalis is nil. The terminal ridge is behind the preoptic recess.

the optic chiasma, as before stated. The considerations regarding the relation of the neural plate to the blastopore brought forward by Kingsbury do not in any way affect this statement regarding the anterior end of the neural plate and tube.

In two previous papers ('09 a, '09 b) the writer has discussed at length the origin of the lateral eyes in the ontogeny of several classes of vertebrates showing: *a*) that they arise as pits near the lateral borders of the neural plate; *b*) that these pits are connected with one another by a groove running across the median plane just behind the terminal ridge, forming there a primitive optic recess, which persists as the recessus postopticus; *c*) that by the development of an obliquely placed optic ridge running upward and backward from the terminal ridge in the wall of the neural tube the optic cups come to be separated from the primitive optic groove and connected by the optic stalks with a recess in front of the optic chiasma in the sphere of the lamina terminalis, the preoptic recess. The oblique optic ridge comes to serve as the bed of the optic tracts in the wall of the thalamus. The derivation of the optic anlagen from lateral areas in the neural plate is supported by Bartelmez ('22) from the study of human embryos. The pineal eye or epiphysis seems also to be formed from the lateral border of the pre-metameric neural plate.

Kingsbury ('20, '22) expresses some doubt whether the postoptic recess is independent from the infundibular recess. That these two recesses exist side by side both before and after the separation of the optic stalk from the primitive optic groove is clear from the accompanying drawings and photographs (figs. 7, 25, 26, 27, 31).

A part of the primitive nervous ectoderm which did not enter into the neural plate but lay close to its anterior border gave rise to the olfactory organ. The numerous cells collected in the olfactory placode perhaps bear some relation to the general sensory nerves of the skin which in lower vertebrates are sensitive to salt and sour. It may be supposed that here adjacent to the anterior end of the neural plate receptive cells of a general chemical sense developed a sensitivity to exceedingly minute quantities of the stimulant and hence became fit to act as distance receptors in the detection of food. If, and so long as the neurenteric canal served as a channel for the ingestion of food the olfactory organ in its position close to the lips of the anterior neuropore may have functioned to test food about to be ingested. After the formation of the palaeostoma and the closing of the neuropore, the functions of a distance receptor became characteristic of the olfactory organs.

In the most primitive living fishes the olfactory centers are of great size and have pouched out laterally to form the beginning of the cerebral hemispheres.

In the pre-metameric neural plate there came about a localization of function of a different pattern from that which produced the four functional columns in the metameric neural tube. In this region the peripheral effective mechanisms were absent and there was no demand for effective centers. What centers or functional areas should be formed and how they should be arranged in the pre-metameric nervous system were determined by three factors: the visual organ, the olfactory organ, and the afferent and efferent tracts connecting the pre-metameric with the metameric neural tube.

The first indications as to the probable primitive arrangement in the neural tube of the forebrain segment are found in the disposition of afferent tracts entering from behind. This point has been discussed in a previous paper ('10 b). In the lowest vertebrates correlating tracts arising from the tactual and proprioceptive centers in the cord and medulla oblongata enter the dorsal part of the diencephalon. Fibers from the gustatory (and general visceral sensory) centers enter the hypothalamus. These facts seem to show that at least in the diencephalon there was a retention of the relative position of the somatic and visceral receptive columns, but that the somatic column was much the larger of the two.

10. This view is supported by the relations of the eyes and the optic tracts. The retinas are derived from areas near the border of the neural plate which clearly fall within the somatic sensory columns as outlined in figure 1. This is true whether the view of the writer ('06, '09 a) or that of Stockard ('13) regarding the locus of the eye-anlage be accepted. They appear to owe their

origin to the multiplication in these areas of the ectodermal cells which are sensitive to light and the heightening of their sensitivity. The fibers which go out from these retinal areas (optic tracts) enter the dorsal parts of the diencephalon and mesencephalon. A large part of these fibers run along the anterior border of the neural plate and cross to the opposite side through the terminal ridge (optic chiasma). If the considerations regarding the extent of the floor plate and epichordal brain be accepted, it is clear that the retinas and the entire course of their central tracts lie wholly within the somatic sensory columns and the area of their confluence across the median plane. Moreover, the centers for the optic tracts in the diencephalon and especially the mesencephalon are in very close relation to the centers for the central tracts of the proprioceptive, tactual, and temperature senses. The grounds for considering the retina and its centers as derivatives of the somatic receptive column in the neural tube are clearer than when they were discussed by the writer in 1905, 1906, and 1909. It should be said, however, that the comparison of the optic tracts with the lemniscus system, because of their crossing in the brain floor, falls to the ground.

We may go one step further and say that in all fishes except cyclostomes, which have not yet been adequately studied, there exists a continuation of the somatic sensory column of the thalamus into the lateral wall of the telencephalon and that fibers arising in the tactual and visual centers of the thalamus enter this region of the telencephalon (Johnston, '11 a, b). This fact offers strong presumptive evidence that the area in question is a primary part of the somatic receptive column. It has recently been shown by Holmgren ('22) that there exists in selachians a well-defined area in the roof of each hemisphere which corresponds to the dorsal or general pallium of reptiles and mammals. My own observations seem to show that this area is continuous with the somatic area in the lateral wall of the telencephalon medium from which the lentiform nucleus develops and that both are related to the corpus callosum in selachians. Thus it appears that the forebrain segment possesses in the fishes generally a clearly recognizable continuation of the somatic receptive column and that in selachians this shows the essential characters of a true general pallium: 1) reception of correlating tracts from tactual, visual, and proprioceptive centers in the metameric brain, 2) morphological unity and clear demarcation from other telencephalic centers (Holmgren), and 3) the possession of a dorsal or pallial commissure independent of the hippocampal commissure and comparable with the corpus callosum of mammals. The presence of this somatic correlating organ in the telencephalon of selachians, the most primitive of the true fishes, is strong evidence that the anlage of the somatic pallium is present from the beginning of vertebrate evolution. The somatic pallium is as old as the olfactory pallium.

11. The visceral receptive column in the typical metameres is the center for receiving general impressions (tactual, thermal, et al.) from the visceral mucosa and muscle-sense impressions from the visceral musculature. To this column also were carried impressions from taste buds when they developed in the entodermal lining of branchial and mouth cavities.[4] When taste buds appeared in the skin they also were supplied by fibers of the visceral receptive nerve-components and all gustatory impressions entered the visceral receptive column.

The taste buds are collections of epithelial cells which are sensitive to chemical stimuli. They differ from the olfactory sense cells in that they require stronger stimulation (i. e., more concentrated solutions) and that they do not send axones into the brain. In the fishes both gustatory and olfactory organs serve important functions in relation to feeding, the olfactory organ in detecting slight or distant indications of food, the gustatory organ in testing the food-object after it has been seized or taken into the mouth. The use of the gustatory organs on the outside of the head and body in the search for food as in many bony fishes is to be regarded as a secondary development. The entrance of the gustatory fibers led to the great enlargement of the visceral receptive column in the region of the medulla oblongata (Johnston, '02 c). From the hypertrophied visceral lobe in the oblongata correlating tracts ran forward to a complex of nuclei at about the level of the isthmus and from these to the hypothalamus (Herrick, '05; Johnston, '11 b). The area in which these tracts end (hypothalamus) appears to be in the territory of the visceral receptive column.

Now it is important to notice that the whole gustatory system is a later addition to the general visceral receptive system. In other words there existed a receptive center for general visceral impressions before the taste buds were developed. It is not surprising that when the taste buds appeared in the entodermal lining of the alimentary canal the fibers which supplied them should find their central endings in the visceral receptive column. Indeed, it would have been very surprising if a separate central column had been developed for the reception of impulses from specialized sense cells in the general visceral surfaces.

Older than the gustatory system, the olfactory organ was the first special sense organ serving for the finding of food and for testing the quality of the water in which the animal lived. It may be supposed that substances in the water (e.g., dissolved minerals or gases) unfavorable to respiration or otherwise deleterious to the life of the animal, would first be detected by the olfactory organ. This is probably the oldest of the special sense organs. The axones of the receptive cells entered the border of the neural plate. When the neuropore closed up the walls of the neural tube which received these fibers hypertrophied and pouched out in response to the incoming stimuli. We cannot say with certainty either that the somatic and visceral receptive columns remained distinct in this anterior end of the neural plate or that the olfactory centers were derived exclusively from either one. The nervus olfactorius and nervus terminalis were the only primary receptive nerves related to the whole forebrain. The one has its receptive cells located in the ectoderm, the other, if sensory at all, is probably general cutaneous. So far as the paradigm of functional columns in the neural tube goes, one would expect both these nerves to be related to the somatic receptive column. What is much more to the point is that the olfactory organ has stimulated the development in the forebrain of large centers peculiar to themselves and that the classification of these with somatic or visceral systems is a matter of convenience.

This olfactory organ plays a remarkable rôle. Arising and remaining in the ectoderm, it primarily serves, not to direct the movements of the animal or to protect it from external objects or enemies as the tactual and visual organs do, but to give information with regard to the chemical or metabolic relations of the animal. The special olfactory centers eventually gain relations to both visceral and somatic receptive columns and the correlating centers derived from them. In the lowest existing vertebrates the olfactory centers send the overwhelming majority of their fibers to the visceral and gustatory centers in the hypothalamus. The hypothalamus becomes in consequence the chief correlating center for olfactory and visceral impressions and the olfactory centers gain their chief directive pathways through the tracts from the hypothalamus to the medulla oblongata. Secondary in importance to these are the tracts, through the habenula, which the writer is inclined to believe is to be regarded as a derivative of the visceral receptive column. Into the habenula, however, come tracts from various sources and here olfactory impulses enter into relation with others belonging to somatic categories. In its earlier evolution, therefore, the olfactory system establishes relations chiefly with the visceral receptive systems and gains its connections with the centers for muscle-control through these visceral correlating centers. Because of these facts and of the apparent primary importance of the olfactory system to visceral activities the writer was led to classify the olfactory organ and centers with the visceral receptive system ('02 c). This view has been accepted by Herrick ('22) and others. The argument about the definition of the term visceral (Dart, '22) I leave to others. The functional and morphological relationships are clear. A rose by any other name would smell as sweet.

A further indication of the intimate association of the olfactory with the visceral receptive column is found in the relations of the tractus pallii in fishes. In addition to the basal forebrain bundle which connects the olfactory centers with the hypothalamus, there is found in selachians, ganoids, and teleosts a sharply defined tract connecting the hypothalamus with the most highly specialized part of the olfactory centers, the portion from which the hippocampus is formed in higher vertebrates. It appears that in the basal bundle descending fibers predominate, while in the tractus pallii fibers arising in the hypothalamus and ascending to the olfactory centers predominate. In whatever tracts they run the existence of ascending fibers from the hypothalamus to the olfactory centers is of great significance. It means that the final correlating centers to which visceral and gustatory impressions are carried in the cerebral hemispheres are at the same time part of the olfactory centers. However much stress we may lay upon the peculiar and individual character of the olfactory apparatus—and the writer is more inclined than heretofore to emphasize this—these olfactory centers serve as the end station for the highest order of correlating fibers carrying visceral and gustatory impressions. The olfactory organ is highly special and independent but its centers and central tracts are most intimately associated with those of the visceral and gustatory organs.

In higher vertebrates important relations are set up between the olfactory centers and the highly specialized correlating centers of the somatic receptive systems, situated in the telencephalon. These relations are already foreshadowed in some of the most active fishes (selachians) by the interchange of fibers between the lateral olfactory area and the anlagen of the lentiform nucleus and pallium respectively. As a result of the development of these olfacto-somatic correlations the olfactory organ changes its mode of functioning. Primitively it gave rise to reflex responses having to do directly with feeding or respiration. In higher forms the olfactory impressions may give rise to such reflex actions, but to an increasing degree such immediate responses are inhibited and the impressions are correlated with those received from the organs of touch, temperature, vision, and hearing to form a whole which we call a percept of the situation or environment at the moment. In this new integration of receptive systems in higher vertebrates brought about chiefly through the evolution of the general pallium, the relationship of the olfactory organ with the somatic receptive and correlating systems comes to be more extensive, if not more intimate, than its relation with the visceral systems. The differentiation of the pyriform lobe and of the newer parts of the amygdaloid complex as a result of this olfacto-somatic relationship has been discussed in the previous section (p. 464 ff.).

B. FORM CHANGES IN THE EVOLUTION OF THE HEMISPHERES

Effect of hypertrophy of the visceral receptive column

In the medulla oblongata of fishes the visceral receptive column is an elongated ridge projecting from the lateral wall into the ventricle. In cyclostomes and selachians this is a rather slender ridge without great enlargement in any part. It is usually largest at about the level of the first roots of the vagus nerve. In some ganoids and teleosts this ridge is greatly enlarged, bulging out into the ventricle and pushing up dorsally until in many cases it thrusts the somatic receptive column to the side. Those changes are especially noticeable in the anterior part of the lobe related to the facial nerve. Those fishes in which this lobe serves chiefly general visceral functions have the vagal portion of the lobe largest, while those fishes in which the taste buds are very numerous have the facial lobe larger than the vagal. In extreme cases the facial lobes not only push dorsally as mentioned, but meet and fuse across the ventricle in the median plane. Some of these conditions are illustrated in previous papers ('06, '11 b).

A similar condition is found in the telencephalon, which helps to explain the form of the hemisphere and the relative position of the functional centers in the telencephalon in early stages of evolution. In Petromyzon a part of the olfactory centers are evaginated into a hollow hemisphere, but that portion into which the tractus pallii comes up from the hypothalamus remains standing vertically in the lateral wall of the telencephalon medium. This structure has been described as the primordium hippocampi ('12 b). Some ground has been given for regarding the ganglion habenulae as an hypertrophied part of the visceral receptive column which has risen dorsally in a similar manner ('11 a).

The tendency for the visceral receptive tissues to rise dorsally in the ventricular wall of the telencephalon accounts for the striking eversion in ganoids and teleosts and for certain relationships in other vertebrates as well. The somatic receptive column has not been recognized in the telencephalon of cyclostomes but in other fishes a condition similar to that described for Petromyzon is found in the telencephalon medium. In selachians along the dorsal border of this region there is a slender continuation of the primordium hippocampi imbedding the posterior pallial commissure and olfacto-habenular tracts, while the ventricular surface down to the recessus preopticus is an olfactory center. Clearly the olfactory centers in the telencephalon medium of selachains present the same relations as in cyclostomes. Just the same situation is found in ganoids and teleosts in the corresponding region ('11 b). In selachians, ganoids, and teleosts the somatic receptive column in this same region is pushed outward and lies on the lateral surface. In the rising dorsally of the olfactory centers and tendency toward eversion the telencephalon medium closely resembles the medulla oblongata in forms with hypertrophied facial or vagal lobe.

In Chimaera (Johnston, '10 d) the telencephalon medium is very greatly elongated and consists almost wholly of fiber tracts. In the massive portion of the forebrain the posterior part is slightly everted like that of teleosts, the anterior part is evaginated and possesses a massive roof like that of selachians. In ganoids and teleosts the tendency to eversion goes farther than in Chimaera so that the whole telencephalon up to the olfactory bulbs is everted like the telencephalon medium of cyclostomes. This is not strictly true, however, in all these fishes, since in Amia (Johnston, '11 b) there is found a true dorsal commissure comparable to the hippocampal commissure of selachians. Practically, however, in ganoids and teleosts the olfactory bulb is the only part which is fully evaginated as hemisphere, the remainder being essentially everted telencephalon medium.

The selachian telencephalon presents a relatively enormous development of the medial olfactory nucleus, which causes the olfactory peduncles to be carried far laterally. Closely related to this is the large size of the tuberculum olfactorium and the pallium. The everted condition of the ganoid and teleost telencephalon is due to the retention and exaggeration of a primitive eversion which belonged to the telencephalon medium. This condition was probably brought about under the influence of the gustatory organs and the tractus pallii which reach their greatest development in these fishes. The continued evagination and the formation of a massive roof in selachians was apparently due to the predominance of the olfactory and somatic systems. The medial nucleus, the tuberculum, and the hippocampal formation in the roof are primarily olfactory. The tractus pallii (gustatory) which comes up to the roof is relatively much smaller in selachians than in ganoids and teleosts. Greater volume for the olfactory centers in selachians was secured by evagination and as the gustatory correlation center was not hypertrophied it exercised only a subordinate influence in determining the form of the brain and was carried into a position in the roof. Since this center had already gained in cyclostomes a position adjacent to the choroid plexus, when it was carried out by evagination in selachians into the hollow hemisphere it retained its morphologically dorsal position and is located in the roof. Likewise the somatic receptive column retains its primitive lateral position and appears in the lateral surface of the telencephalon medium and in a dorso-lateral position in the roof of the hemisphere (Holmgren, '22). The greater importance of the somatic centers in selachians is probably a strong factor in producing an evaginated hemisphere in the place of an everted telencephalon medium. The expansion of the somatic area in the lateral wall favored a continuation of the evagination process by which the olfactory bulb was formed. It would be of the greatest interest to know the morphology and history of the centers in ganoids and teleosts corresponding to the general pallium described by Holmgren.

Professor Holmgren's very valuable paper ('22) reveals an organization in the selachian forebrain which heretofore has been regarded as characteristic of that of higher vertebrates. He recognizes well-defined areas in the developing forebrain of Acanthias which are clearly comparable morphologically with well-known areas in the reptilian and mammalian brain. The identification of an hippocampal formation and a general cortex and the demonstration that each of these is continuous with its fellow of the opposite side through a bridge of tissue across the median plane, are invaluable additions to our knowledge of forebrain morphology.

It seems to the writer that Professor Holmgren has been unfortunate in his identification of the pyriform cortex. This cortex as described lies in the brain wall in front of the olfactory peduncle extending from the peduncle along the lateral and rostral wall of the frontal evagination or pouch. This topographically rostral region clearly belongs to the morphological medial wall of the brain, and its constituent parts are to be compared with structures lying in the medial or septal wall in the brain of a chelonian, marsupial, or mammal.

This view is clearly stated by Professor Holmgren in the second paragraph of page 399. In response to a letter from the present writer pointing out the inconsistency between that paragraph and the interpretation of a certain area as pyriform cortex, Professor Holmgren inserted in the manuscript the third paragraph on page 399, setting forth the hypothesis that the primary situation of the bulbus is a lateral one and that except in selachians the bulbus is dislocated during ontogeny to a terminal position. This hypothesis I cannot accept. It is undoubtedly true that the bulbus pediment moves from a more lateral to a more rostral position during ontogeny in various forms including some selachians, but I know no reason for considering this to be a dislocation or relative shifting of parts. The different (topographical) position of the bulbus in different forms is due to the differences in relative size of development of the centers or areas surrounding it. The bulbus is placed far laterally in selachians because of the relatively enormous size of the medial olfactory area, the tuberculum olfactorium, and the pallium. The apparent wandering of the bulbus in other forms toward the median plane which brings it into a (topographical) terminal position is due to the reduction of the medial olfactory center and tuberculum olfactorium and the increase of the lateral olfactory area and spreading of the general cortex laterally. No wandering of the bulbus takes place, but only a relative reduction of centers medial to it and enlargement of centers lateral to it. By common usage the bulbus olfactorius has been accepted as the mark of the morphological frontal pole, and it marks this pole just as truly in selachians where it is lateral in position as it does in teleosts and reptiles where it is rostral in position (I would not apply the word 'terminal' to the olfactory bulb because of confusion with the true anterior end of the brain at the terminal ridge or optic chiasma.)

The author describes a zona limitans medialis bounding the hippocampal formation medially, and a zona limitans lateralis bounding the pyriform cortex laterally. The relations of these two zonae limitantes is thus clearly described:

"Below the ventricle is a clear space crossing over the ventral part of the brain and delimiting the nucleus olfactorius lateralis and the tuberculum olfactorium cortex which lie below it. This space, poor in cells, medially bends up dorsad to the medial border of the hippocampal rudiment. The dorsal part of this clear space in the future development is destined to become the zona limitans medialis (*z. l. m.*). The lateral part of the space in question also bends dorsad to the lateral border of the pyriform lobe and forms the zona limitans lateralis (*z. l. l.*). Thus at the front pole of the forebrain vesicle the zona limitans medialis and lateralis unite" (p. 405). On page 406 it is shown that what is called the zona limitans lateralis bends upward to pass over the olfactory crus. The reader of Holmgren's paper will do well to remember that figures 5 to 15 and 17 to 20 from transverse sections of the forebrain of Acanthias embryos are taken in front of the bulbus olfactorius and therefore represent only the rostral pouch of the medial brain wall.

Thus the pyriform cortex of Holmgren lies in the topographical rostral and lateral wall of the rostral evagination of the hemisphere in front of the olfactory bulb. It ends at the level of the olfactory bulb in contact with the rostral end of the lateral olfactory nucleus. Now in reptiles, marsupials, and mammals the pyriform lobe lies in the lateral wall of the brain caudal to the olfactory bulb and represents a portion of the lateral olfactory nucleus lying along the lateral border of the general pallium and modified in function and structure because of that relationship. The 'pyriform lobe' here described lies in the topographically rostral wall in front of the bulbus olfactorius and therefore in the morphologically medial wall. Moreover, this 'pyriform cortex' is continuous around the rostral surface with the hippocampal formation. Thus in the 4.5 cm. stage, "in the foremost part of the forebrain the pyriform cortex and the hippocampal cortex rudiment are constantly continuous with each other" (Holmgren, p. 403). This foremost part or pole of the brain where also "the zona limitans medialis and lateralis unite" is, however, the topographical and not the morphological frontal pole.

All these facts show clearly that what is found in Professor Holmgren's sections is a continuous mass of cells bordering the general pallium medially and rostrally as far as the bulbus olfactorius. To the medial portion of this he has rightly given the name hippocampal formation. The lateral part also belongs to the hippocampal formation and throughout its extent it is bounded ventrally by a cell-free space which lies wholly in the morphological medial wall and is the zona limitans medialis. A zona limitans lateralis, if present, is represented by the doubtful or indistinct cell-free space in the lateral wall caudal to the bulbus olfactorius.

A very important relation of the hippocampal formation which has been clearly recognized since Elliot Smith's work on the marsupials is obscured by Professor Holmgren's description for the selachians. I refer to the fact that the hippocampal formation extends right forward to the olfactory crus. This is clearly true also in Acanthias if the region described as pyriform cortex be interpreted as part of the hippocampal formation. Holmgren (p. 399) regards this extension of the hippocampal formation directly to the olfactory crus as a secondary condition, but this is only because he names this rostral part of the hippocampal formation in selachians the pyriform cortex. Of the true pyriform lobe developed from the lateral olfactory area Holmgren takes no cognizance.

The accompanying drawings (figs. 2 to 18) from a series of transverse sections and from a series of sagittal sections of the forebrain of Squalus acanthias of about 48 mm. serve to confirm Holmgren's description of pallial areas. The sagittal sections show especially well the continuity of the hippocampal formation from the median commissure bridge right round the rostral pouch to the base of the olfactory bulb. Further comments on the pallial areas which appear in these figures are made on a later page.

The interpretation here suggested makes possible a direct and simple comparison of the general pallium and hippocampal formation of Acanthias with those of a primitive reptile such as the turtle.

The amphibian telencephalon is characterized by an evagination nearly as complete as that of reptiles together with an arrangement of commissures closely comparable with that of ganoids and teleosts. The fact that the hippocampal commissure crosses beneath the ventricle shows the affiliation of the amphibians with primitive ganoid-like ancestors. That the amphibians did not follow their ancestors in having the forebrain everted is accounted for by the sharp and probably sudden reduction in the gustatory system when the amphibians came to live on land. The primitive eversion has been retained in the telencephalon medium and in the arrangement of the commissures (Johnston, '06, '10 c, '11 b), but the olfactory organ, being well developed and the new mode of life demanding a large development of the somatic centers, the anterior part of the forebrain continued to evaginate very much as it does in selachians and reptiles. The posterior part of the telencephalon showing ganoid type of structure remains short while the evaginated part becomes greatly elongated. The amphibian telencephalon has been determined by a peculiar set of circumstances or a peculiar series of stages and it throws little light on the evolution of the hemispheres in higher vertebrates.

The selachians on the other hand, or selachian-like fishes, are undoubtedly the ancestors of reptiles, birds, and mammals. It is unfortunate that we have not a more complete account of the telencephalon of dipnoans, but enough is known (Kerr,

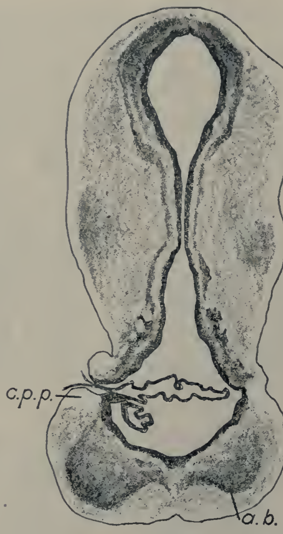


Fig. 2

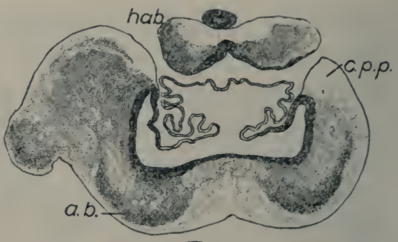


Fig. 3

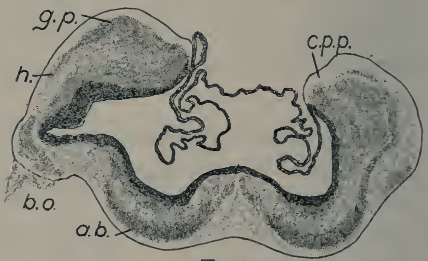


Fig. 4

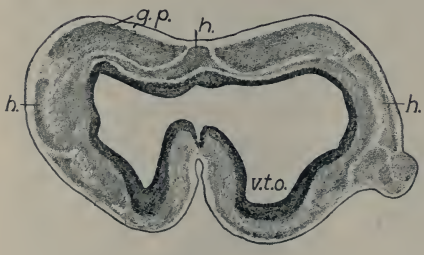


Fig. 5

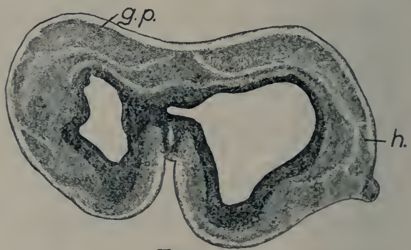


Fig. 6

Figs. 2 to 6 Transverse sections of the telencephalon of a Squalus acanthias embryo of 47.3 mm. Scammon no. 11. × 15 diam.

Fig. 2 Section taken at the junction of telencephalon and diencephalon. The upper part of the figure shows part of the thalamus and midbrain. Note that the dense cell lamina of the basal area extends back to this level. The cell-free area at the dorsal border of the telencephalon imbeds both the posterior pallial commissure (*c.p.p.*) and the stria medullaris.

Fig. 3 On the left side the section touches the caudal surface of the olfactory bulb. The thick brain wall to which the bulb is attached probably includes parts of the lateral olfactory area and general pallium.

Smith, Holmgren) to show that they possess a true dorsal pallium and commissure comparable with the hippocampal formation of reptiles. A somatic pallium seems also to be present but less developed than that of reptiles. The dipnoan forebrain belongs clearly to the selachian-reptilian-mammalian type and not to the ganoid-teleost-amphibian side branch. (Figure 90 of '11 b requires revision on this point.) To understand the evolution of the mammalian forebrain we must follow the changes of form and structure in selachians, dipnoans, reptiles, and marsupials and try to see the influence of changes in habits and environment in bringing about those changes in structure.

Extent or degree of evagination

As already noticed, in cyclostomes the bulb and part of the olfactory centers are evaginated, while the primordium hippocampi remains in the telencephalon medium. In Chimaera the evagination is somewhat greater. In ganoids and teleosts eversion becomes the dominant feature, while in amphibia, with the reduction of the gustatory apparatus, the eversion is subordinated to an evagination parallel with that in dipnoans and reptiles.

In selachians most of the olfactory central mechanism is evaginated, but the telencephalon medium retains a slender continuation of the primordium hippocampi (figs. 2, 3) and has a large part of the somatic column. The latter is destined to form the lentiform nucleus. Holmgren has not recognized this 'somatic area' in selachians, mistaking it for "part of an unusually

Fig. 4 On the left side the section passes through the olfactory bulb. The right side is still behind the bulb. The letter *h* marks the extreme lateral part of the hippocampal formation which meets the rostral side of the bulb. It is this which Holmgren calls the pyriform cortex.

Fig. 5 A section much farther forward, the right half of which touches the rostral surface of the bulb. The lower part of the ventricle corresponds to the ventricle of the tuberculum olfactorium in mammalian embryos. In the upper wall the hippocampal formations of the two sides meet in a median bridge as shown by Holmgren in his figure 15. The artist has not exaggerated the distinctness of the pallial areas in this specimen.

Fig. 6 A section a little farther forward than the last which shows the laminae of the general pallium meeting in the median plane. Rostral to this the general pallium disappears and the hippocampal formation extends across the upper part of the sections.

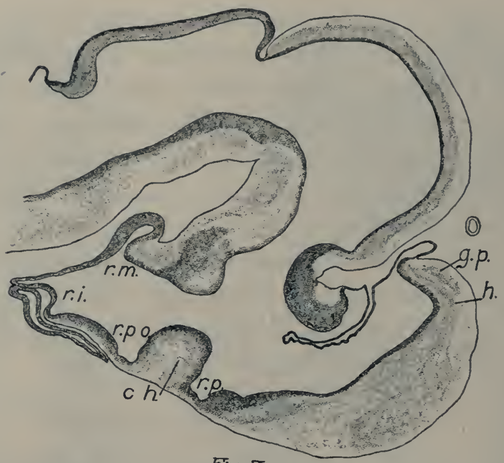


Fig. 7

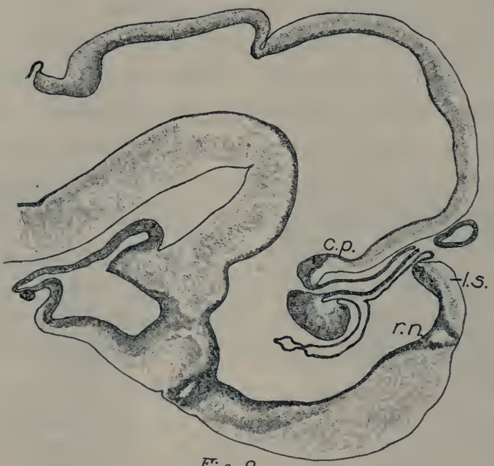


Fig. 8

Figs. 7 to 18 Drawings from a series of sagittal sections of an embryo of Squalus acanthias of 48 mm. Scammon. × 16. Figure 7 is in the median plane in the hypothalamic region; figure 8 is median at the neuroporic recess. The following sections extend to the olfactory bulb.

Figure 7 shows very clearly the distinctness of the postoptic recess and the infundibular recess. Figures 8 to 18 show the pallium extending from the bridge in the median plane to the olfactory peduncle. The pallium is bounded ventrally by a continuous zona limitans medialis (Johnston, '11 a) from the median plane to a point near the peduncle. Corresponding to this cell-free zona is a well-marked ventricular sulcus (*s.l.*). The bridge of pallial tissue which crosses the median plane in the lamina supraneuroporica (fig. 8, *l.s.*) contains both hippocampal and general

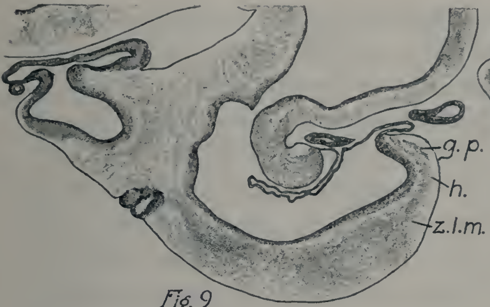


Fig. 9

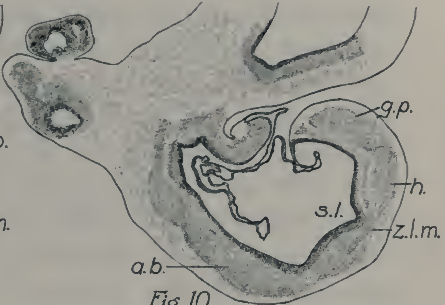


Fig. 10

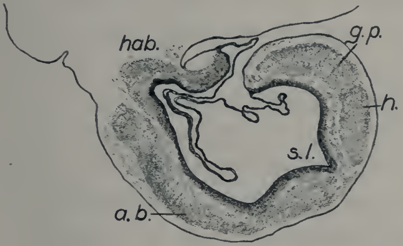


Fig. 11

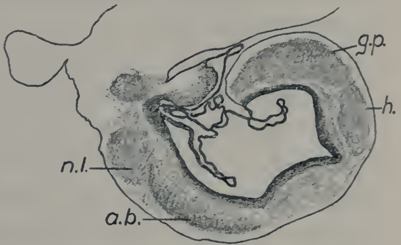


Fig. 12

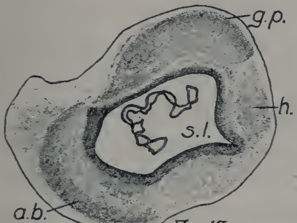


Fig. 13

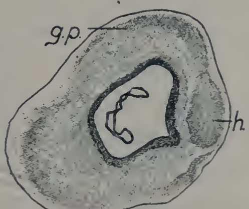


Fig. 14

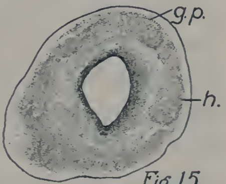


Fig. 15

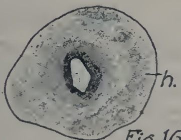


Fig. 16

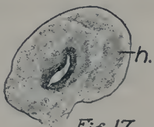


Fig. 17

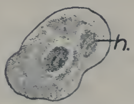


Fig. 18

pallial elements. This lamina supraneuroporica is to be compared with that of cyclostomes (Johnston, '12 b, fig. 23), and with that of the turtle, opossum, bat, and man ('13 b, figs. 5, 22, 25, 8).

A short distance from the median plane (fig. 9) the general pallial and hippocampal masses become distinct and are clearly distinguished through all the following figures to the base of the olfactory bulb. The hippocampal formation is a continuous mass from the median plane to the bulb. It is the lateral part of this which Holmgren calls the pyriform lobe. It is instead to be compared with the rostral extension of the hippocampal formation in reptiles, marsupials, and mammals which reaches to the olfactory bulb.

large nucleus preopticus." Its extent is clearly defined on page 12 of '11 a. Through this lentiform nucleus runs the primitive crus cerebri consisting of thalamic projection fibers (tactual, visual, etc.) to the somatic pallium and the descending fibers from the pallium. While the large fundamental divisions of the hemisphere can be recognized here, these parts have very different place relations in selachians and mammals. In selachians the pallium—including somatic and visceral parts—lies forward from the lentiform nucleus, the lateral olfactory area extends from the olfactory peduncle caudad lateral to the pallium to meet the lentiform nucleus. In the base, the anterior commissure crosses at about the caudal border of the lateral olfactory area and the tuberculum olfactorium lies forward from this commissure and connects the lateral and medial olfactory areas. In mammals the great occipital and temporal poles lie behind the level of the anterior commissure and lentiform nucleus and are occupied by somatic pallium and hippocampal formation and by pyriform lobe and amygdaloid complex which have been derived from the lateral olfactory area and tuberculum olfactorium.

Not only is the great size of the somatic pallium the chief characteristic of the mammalian forebrain, but the growth of this somatic pallium has been the dominating influence in the rearrangement of parts in the telencephalon from the selachians onward. The increasing importance of the thalamic radiations and the somatic pallium led to the enlargement of the lateral olfactory area and the evolution of the pyriform lobe and amygdaloid complex as described in section IV. At the same time the simple function of the olfactory apparatus as a distance receptor in finding food diminished in importance and the large medial olfactory nucleus was relatively reduced. The expansion of the general pallium in its lateral position caudal to the olfactory peduncle and the reduction of the medial olfactory nucleus in front of the peduncle brought the olfactory bulb into its characteristic rostral position near the median plane.

The further expansion of the hemisphere involved a bending laterad of the crus cerebri and of the lentiform nucleus through which it passes, and a narrowing of the interventricular foramen in such a way that the medial walls of the hemispheres approach one another closely and the corpus striatum becomes the floor of the lateral ventricle. There is nothing complex or intricate about the behavior of the lentiform nucleus or the crus in the evolution of the hemisphere. The crus bends laterad because the pallium expands backward. The lentiform nucleus increases in volume because it, too, is concerned in the increased functions of correlation of which the pallium is the chief mechanism. The volume of the corpus striatum is further increased by the increased number of fibers in the crus. Finally from reptiles onward the nucleus caudatus is added to the corpus striatum by immigration from the border of the pallium. The thickening of the crus led to the attenuation of the nucleus caudatus and of the bed of the stria terminalis as explained in section I. The crus and lentiform nucleus form a relatively rigid and unchanging stem attaching the hemisphere to the thalamus as long ago explained by His. What remains to be explained is the movement of other parts due to the expansion of the somatic pallium.

As the pallium expanded backward the lateral olfactory area elongated with it and came to cover the lateral surface of the lentiform nucleus and crus. This condition is seen during the ontogeny of reptiles (Johnston, '16 b). Later in the ontogeny the cells of the lateral olfactory area are pushed aside by the bulging out of the crus and recede to the borders of the striatal area leaving the bundles of the crus visible from the lateral surface. In marsupials the lateral olfactory area (lobus pyriformis) maintains its position covering the striatum laterally in the adult. In mammals this condition is gradually changed by the growth of the pallium so that the lobus pyriformis is pushed down on to the basal surface and the striatum is covered by pallium, thus producing the true insula. Finally, the insula is covered in by the opercula which bound the sylvian fissure.

The expansion of the somatic pallium carried the hippocampal formation with it more or less mechanically. The hippocampus in reptiles forms a broad curved band along the medial border of the dorsal pallium and bending down into the temporal pole. Later, through the pressure from the general pallium and the thickening corpus callosum the dorsal hippocampus was compressed and attenuated as shown by Elliot Smith in his early work. The hippocampus generally in mammals maintains its continuation forward beyond the corpus callosum to the base of the olfactory peduncle.

Caudally when the hemisphere extends beyond the level of the telencephalon medium and bends down to form the temporal pole, the structures which cover the ventricular surface of the lentiform nucleus and crus become involved in this pole. For the explanation of this the fact that the nucleus caudatus bends over the crus into the temporal lobe is of little importance, since this nucleus is derived from the lateral border of the pallium and merely follows that border. The structures found in selachians on the internal surface of the telencephalon medium are: the continuation of the hippocampal formation imbedding the posterior pallial commissure, the ventricular gray corresponding to the lateral olfactory area which becomes the bed of the stria terminalis, and other olfactory gray related to the preoptic region and imbedding part of the stria medullaris (tractus olfacto-habenularis). The disposition of the stria medullaris in marsupials and mammals shows that this latter tissue is not carried out into the hemisphere. Great bundles of the stria medullaris arise from the medial forebrain bundle, the preoptic region and the adjacent parts of the thalamus (see sections I to IV, figs. 23, 24). The bed of the posterior pallial commissure in reptiles is carried down over the latero-caudal surface of the internal capsule, and the posterior pallial commissure runs up from the hippocampal formation with the temporal pole components of the stria medullaris. The bundles of the stria medullaris arising from the nucleus of the lateral olfactory tract, from the lateral border of the tuberculum olfactorium, from the lateral olfactory area (pyriform cortex), and the hippocampus are still present in the temporal pole at least in marsupials (Didelphys). The bundle from the hippocampus is homologous with the posterior pallial commissure of selachians.

The olfactory tissue which becomes the bed of the stria terminalis is elongated with the pallium and the lateral olfactory area and bends down into the temporal pole as described in earlier sections. This tissue remains massive behind the crus and gives rise to the central and medial amygdaloid nuclei, while it becomes attenuated over the crus where the stria terminalis fibers are accompanied by only a little gray matter.

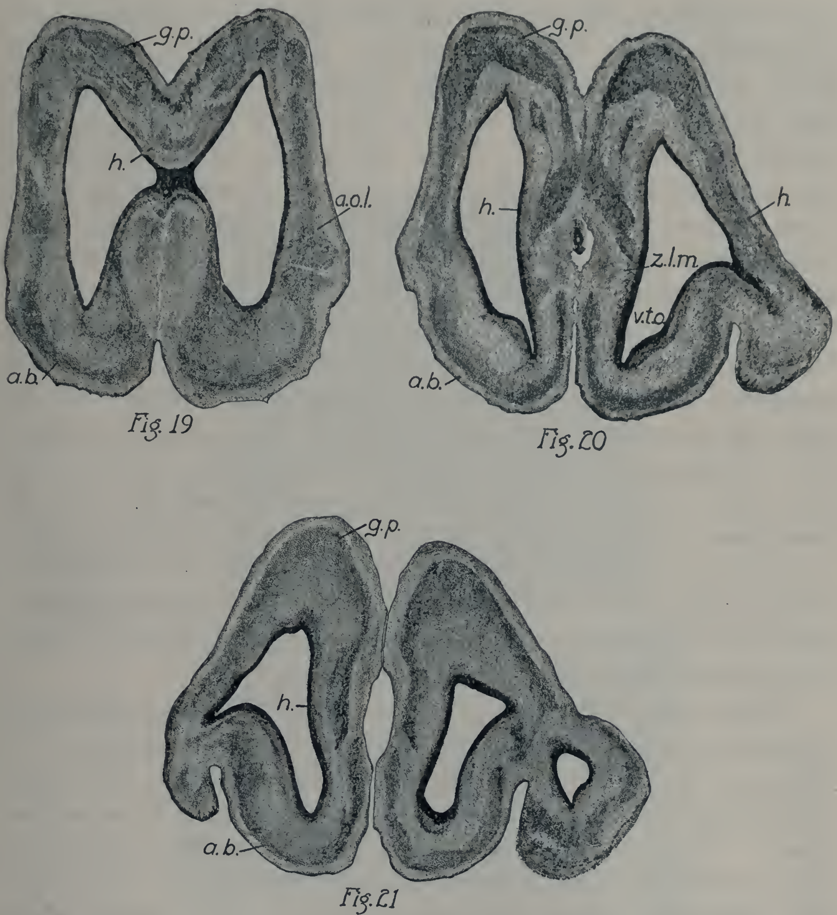
The continuity of lateral and medial olfactory areas is maintained throughout the evolution of the hemispheres through the derivatives of the basal area of the selachian, namely, the tuberculum, anterior perforate space and diagonal band. As the hemisphere expands these structures are elongated and undergo some differentiation. The tuberculum and anterior perforate space owe their importance to the fact that they enter into the olfacto-somatic correlation system. The diagonal band becomes the chief avenue of connection between the more strictly olfactory portions of the amygdaloid complex and the hippocampus and medial olfactory areas. The relations of the anterior commissure to these structures are not materially changed in the vertebrate series. Its pallial elements run beneath the internal capsule and bend back in the external capsule to the temporal pole. These are especially strongly developed in marsupials and are important in mammals. (See '13 b, p. 402, for a discussion of the anterior commissure in relation to the corpus callosum.) The lateral olfactory component of the anterior commissure is represented by the commissure of the nucleus of the lateral olfactory tract which forms a bundle of the stria terminalis. To what extent the temporal limb of the anterior commissure carries fibers arising in amygdaloid nuclei has not been determined.

It is not within the scope of this paper to discuss the evolution of the structure of the general pallium. That the essential homologue of the general pallium was present in selachians seems established by the work of Holmgren ('22) which the writer can confirm.

Figures 2 to 6 show two points of interest: the prolongation of the basal area far back into the telencephalon medium, and the differentation of the pallial areas, each of which is confluent with its fellow across the median plane at the level of the neuroporic recess and forward. The disposition of the basal area should be compared with that of the cell-proliferation in the human embryos of 21 mm. which gives rise to the tuberculum olfactorium, diagonal band and anterior perforate space (see sections I to IV, figs. 1 to 16). Figures 7 to 18 show the disposition of the pallial areas in sagittal sections of a 48 mm. Squalus. It is noteworthy that both of the pallial areas cross the median plane and that the deeper one continues around the rostral wall without break to enter the olfactory peduncle just as the hippocampal formation does in mammals. Figures 19, 20, 21 show the same two pallial areas in a young pup of Scymnus. In their general arrangement the pallial areas of both Squalis and Scymnus show a fundamental likeness to the hippocampus and general pallium of reptiles, especially the more primitive turtle. The hippocampus lies just above the level of the neuroporic recess and is separated from the medial olfactory (parolfactory) area by the medial sulcus limitans hippocampi and extends to the olfactory peduncle. It is the lateral part of this structure adjacent to the olfactory peduncle with Holmgren has identified with the pyriform cortex (p. 170).

The continuity of the hippocampal and general pallial cortical areas across the median plane is very interesting in relation to the problem of cortical commissures, the hippocampal commissure and the corpus callosum. We shall await with interest Holmgren's report on the fiber relations in embryonic selachians to determine whether the bridges of cellular tissue described are the beds respectively for the two cortical commissures.

It is important to recognize that this general pallium was established and clearly distinct from the olfactory centers in selachians. Elliot Smith ('10, '19) and Herrick ('10, '21) have maintained the view that the general pallium (neopallium) arose from olfactory area because of the penetration of thalamic radiations into regions which were primarily olfactory. Since the work of Holmgren it is no longer necessary to discuss whether the pallium has arisen in amphibians or even in dipnoans. Already in selachians the general pallium is clearly present in simple form and independent of the olfactory centers. This seems to leave no ground for the theory that the neopallium has been differentiated



Figs. 19, 20, 21 Three transverse sections of the telencephalon of Scymmus lichia of about 150 mm. length. Figure 19 falls immediately in front of the interventricular foramen and behind the olfactory bulb. Figures 20 and 21 fall successively farther forward, passing through the olfactory bulb. In figure 19 both hippocampal and general pallial layers enter into a thick median (commissural) bridge. The lateral olfactory area which appears lateral to the basal area (tuberculum) is properly to be compared with the pyriform lobe of higher forms. Figure 20 shows the neuroporic recess in the center, at either side of which the zona limitans medialis is clearly marked. The hippocampus in figures 20 and 21 occupies the same position as it does in reptiles. All three sections show the basal area of wide extent very much as in adult selachians. The ventricular pouch (*v.t.o.*) descending into this area should be compared with the ventricle of the tuberculum olfactorium in mammalian and human embryos (figs. 13 and 14 in section I).

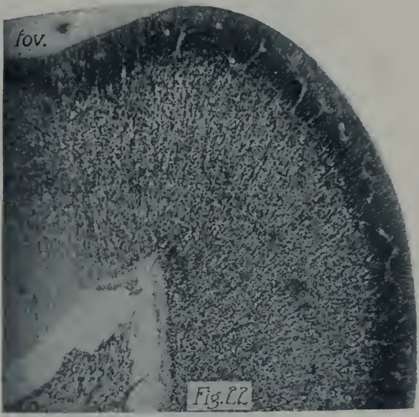
out of olfactory centers under the influence of thalamic radiations penetrating those olfactory centers. The thalamic radiations from somatic centers are already present in selachians, ganoids, and teleosts (Johnston, '11 a, b) and they penetrate centers which are not olfactory. These centers are to be regarded as primitive somatic correlating centers which give rise to the lentiform nucleus and the general pallium in higher forms. The special commissure of the centers in selachians I have compared with the corpus callosum ('11 a).

The evolution of the general pallium proceeds more rapidly than has generally been supposed. Whereas there has been serious discussion (P. Ramon, Edinger, Meyer, Unger, Cajal) of the question whether a true representative of the general pallium is to be found in reptiles, the writer has shown ('15 b, '16 b) not only that a histologically differentiated pallium is to be recognized, but that along the anterior and lateral border of this is found an area which is structurally characterized by thickening and by larger size of its cells, an area which upon electrical stimulation proves to be the equivalent of the excitable ('motor') cortex of the mammalian hemisphere.

For this area Miss Crosby ('17) proposed the term primordium neopallii and Elliot Smith ('19) gives his hearty approval to this new term. But the application of this term to the pallial thickening in reptiles is too conservative by at least a few million years. We cannot properly speak of a neopallial primordium in any animals higher in the vertebrate scale than the selachians. The pallial thickening of reptiles is not only not a primordium from which the general pallium of mammals is evolved, but is a specialized part of the general pallium, namely, the so-called motor area probably homologous with the precentral area in man. The neopallium in reptiles is by no means in a primordial stage but has already a broad extent with localization of functions.

This position of the excitable pallium in the turtle agrees well with the condition in lower mammals where, as is well known, the excitable cortex is located far forward. The larger posterior part of the cortex in reptiles or mammals develops into the general sensory, proprioceptive, visual, auditory, and associational areas.

The frontal lobe which appears to have aesthetic and emotional functions in man develops later from tissue lying between the excitable area and the olfactory bulb. The relatively enormous development of this in man brings the olfactory bulb upon the basal surface of the frontal lobe.



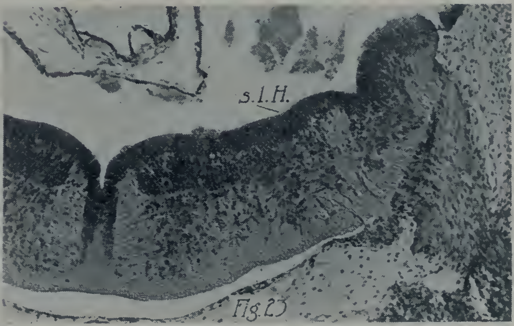
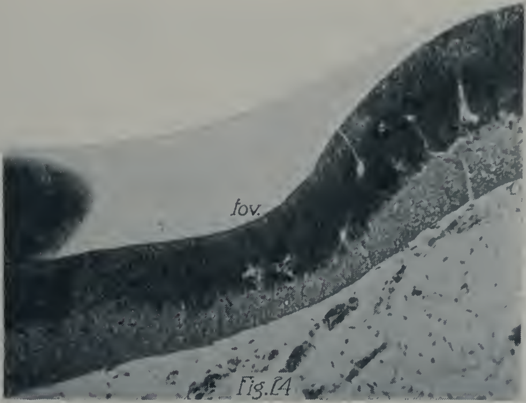


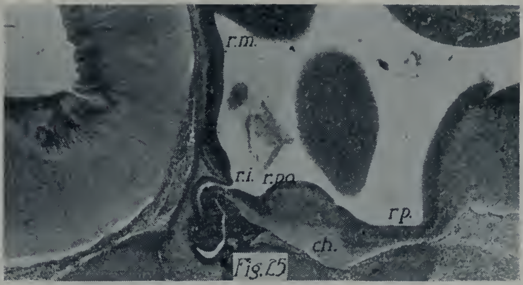
Fig. 22 Sagittal section of the brain floor of a sheep embryo of 22 (?) mm. Minn. Anat. 533. × 24. The photograph shows the structure of the brain floor forward from the fovea isthmi. Compare with the upper portion of Kingsbury's figure 7. The vertical fibers are comparable to the raphé fibers in and behind the fovea but are less numerous and are infiltrated by a larger number of cells.

Fig. 23 Transverse section of the brain of Squalus acanthias embryo of 33.1 mm. at the level of the seventh nerve roots, to show the relations of the sulcus limitans. of His. The section also shows a typical raphé. Scammon no. V. × 46.

While for some years the attempt to make direct comparison between the human forebrain (diencephalon and telencephalon) and that of lower vertebrates fell into disrepute, this was because of the limited knowledge (partly due to the limited technique) upon which the comparisons by early authors (Rabl-Rückhard, Edinger, Studnicka, Osborn, and others) were based. We have now a fairly complete solution of the head problem and of the relation of the neural plate to the blastopore, as well as a large collection of detailed and reliable data upon the structure, neurone connections, and embryology of the anterior regions of the brain. The farther this latter work has proceeded the more clear has become the continuity of phylogenetic development of brain structure. New structures have not appeared, and although old structures have been modified, the process of evolution leading to the human brain has been one of gradual development of the elements inherent in the structures or areas laid down in very early vertebrate ancestors with gradual shifting of emphasis, growth, or decline of this or that element, all under the influence of environment and changing habits. This is true of the following structures, of each of which we now have a fairly complete history; medial and lateral olfactory centers and hippocampal formation; amygdaloid complex; corpus striatum including putamen, globus pallidus, nucleus caudatus, bed of stria terminalis; general cortex or neopallium; and the fiber systems connecting the telencephalon with lower centers. Future studies must be directed to the details of the differentiation of these structures and their modification in response to changes in environment, habits, and peripheral sense organs.

The attempt to draw a diagram of the relations of somatic and visceral receptive columns in the forebrain region (fig. 1) may be premature. It may not be possible to determine the primitive relations of these columns in the forebrain. It is the writer's present opinion, however, that a differentiation of these functional areas had taken place in the ancestors of vertebrates at a stage before the rolling up of the neural plate into a tube; that the axones of olfactory cells scattered in the skin found connections with neurones in the anterior end of the visceral





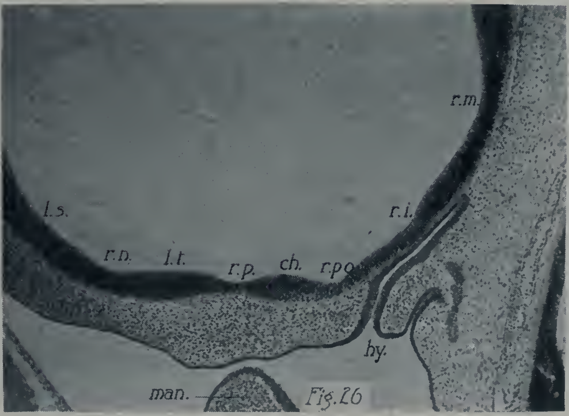


Fig. 24 Sagittal section of the brain floor of a human embryo of 15 mm. C. R. H. 35 Minn. Anat. × 110. The photograph shows that the raphé fibers extend forward beyond the fovea. The anterior end is to the right.

Fig. 25 Sagittal section of a pig embryo of 24 mm. Anat. 508. × 24. The section shows the raphé at the level of the pons. In the floor of the diencephalon the recessus postopticus and recessus infundibuli are clearly distinct.

Fig. 26 Sagittal section of a pig embryo of 9 mm. in the region of the lamina terminalis and floor of the diencephalon. Anat. 464 × 60. To show the pre- and postoptic recesses in relation to the terminal ridge which becomes the chiasmatic ridge. Note that the recessus infundibuli is quite distinct from the postoptic recess.

receptive column; that general cutaneous ganglion cells established connections with the anterior end of the somatic receptive column; and that these two columns were more or less crowded and crumpled as the neural plate was rolled up into a tube. In the neural tube stage and in connection with all the changes attendant upon the development of the branchial apparatus and the abandonment of the palaeostoma in favor of the gnathostoma the rostral cutaneous area was greatly reduced and the innervation of most of it was taken over by the trigeminus. (Or, perhaps it is sufficient to say that the area innervated by the nervus terminalis was reduced to an insignificant vestige.) This situation left the anterior end of the somatic receptive area without dominating peripheral sensory fibers, such as enter all other segments of this column. The want of incoming sensory impulses of the first order, however, did not result in atrophy of this central area because it was already penetrated by secondary fibers coming up from lower segments of the same column, namely, visual, cutaneous, and proprioceptive centers. These secondary connections reaching the most anterior portion of the somatic receptive column maintained the functional activity of that region and pari passu with the reduction of its cutaneous area transformed it from a cutaneous center into a correlating center for all forms of receptive impulses coming to the somatic column from the skin and sense organs derived from the skin in all the more caudal segments. This process by which the anterior

Fig. 27 Sagittal section of an embryo of Chelydra serpentina of 8½ mm. carapace. Johnson. × 20. The section shows the independence of the recessus postopticus and the recessus infundibuli. The section is not quite median in the region of the fovea isthmi and tuberculum posterius.

Fig. 28 Sagittal section of an embryo of Amblystoma tigrinum of about ten somites to show the relation of the notochord to the brain floor. × 46. The primitive hypothalamic downgrowth (*hyth*) is indicated by a thickening of the brain floor in which are seen two small cavities or clefts. These clefts communicate with the ventricle, but are irregular so that their connection does not show in a single section. The anterior end of the notochord is fairly sharply marked at the letters *nch*. The dense collection of small cells immediately above the letters *nch.* among which are several mitotic figures probably form the caudal wall of the hypothalamus.

Fig. 29 Sagittal section of an embryo of Amblystoma tigrinum of about seventeen postotic somites to show how the anterior part of the brain has been carried forward, leaving the anterior end of the notochord beneath the medulla oblongata. × 46.

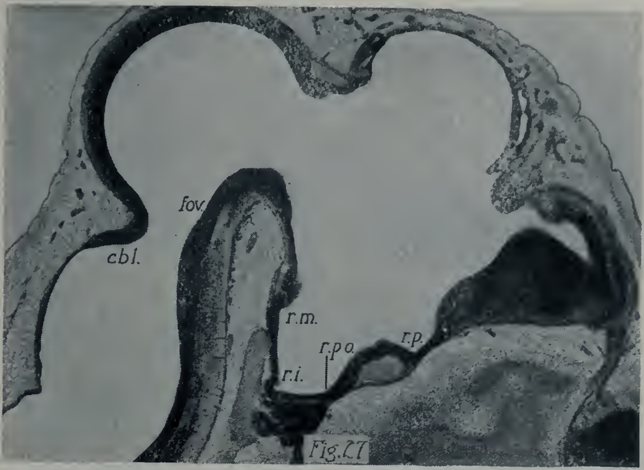


Fig. 27

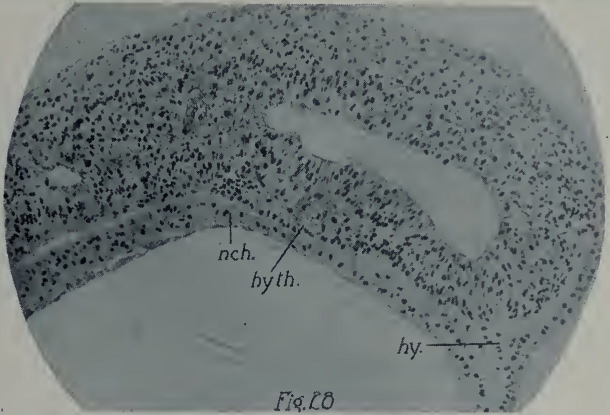


Fig. 28

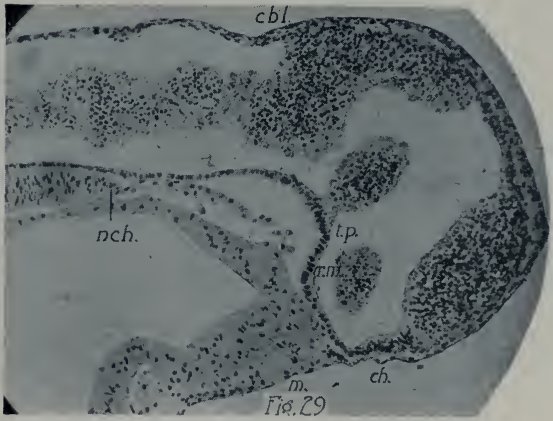


Fig. 29

segment of the somatic receptive column was transformed into a somatic pallium or general cortex has been discussed at greater length in an earlier paper ('10 b). Although on pages 163 to 167 above I have refrained from speculation in treating of the olfactory centers, it has seemed worth while to state here at the end what I think is the most probable explanation of the origin of the olfactory and general (somatic) pallia.

November 20, 1922.

LITERATURE CITED

Bartelmez, G. W. 1922 The origin of the otic and optic primordia in man. Jour. Comp. Neur., vol. 34.

Burr, H. Saxton 1922 The early development of the cerebral hemispheres in Amblystoma. Jour. Comp. Neur., vol. 34.

Crosby, Elizabeth C. 1917 The forebrain of Alligator mississippiensis. Jour. Comp. Neur., vol. 27.

Herrick, C. Judson 1905 The central gustatory paths in the brains of bony fishes. Jour. Comp. Neur., vol. 15.

1910 The morphology of the forebrain in amphibia and reptilia. Jour. Comp. Neur., vol. 20.

1922 What are viscera? Jour. of Anatomy, vol. 61.

Holmgren, Nils 1922 Points of view concerning forebrain morphology in lower vertebrates. Jour. Comp. Neur., vol. 34.

Johnston, J. B. 1902 c An attempt to define the primitive functional divisions of the central nervous system. Jour. Comp. Neur., vol. 12.

1906 Nervous system of vertebrates. Philadelphia: Blakiston.

1909 b The morphology of the forebrain vesicle in vertebrates. Jour. Comp. Neur., vol. 19.

1910 b The problem of the correlation mechanisms. Anat. Rec., vol. 4.

1910 c The evolution of the cerebral cortex. Anat. Rec., vol. 4.

1910 d A note on the forebrain of Chimera. Anat. Anz., Bd. 36.

1911 a The telencephalon of selachians. Jour. Comp. Neur., vol. 21.

1911 b Telencephalon of ganoids and teleosts. Jour. Comp. Neur., vol. 21.

1912 b The telencephalon in Cyclostomes. Jour. Comp. Neur., vol. 22.

1913 b The morphology of the septum, hippocampus, and pallial commissures in reptiles and mammals. Jour. Comp. Neur., vol. 23.

1915 b The cell masses in the forebrain of the turtle, Cistudo carolina. Jour. Comp. Neur., vol. 25.

1916 a Evidence of a motor pallium in the forebrain of reptiles. Jour. Comp. Neur., vol. 26.

1916 b The development of the dorsal ventricular ridge in turtles. Jour. Comp. Neur., vol. 26.

Kingsbury, B. F. 1920 The extent of the floor-plate of His and its significance. Jour. Comp. Neur., vol. 32.

1922 The fundamental plan of the vertebrate brain. Jour. Comp. Neur., vol. 34.

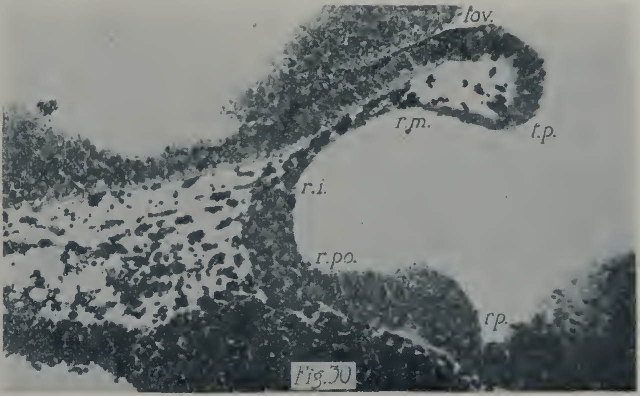


Fig.30

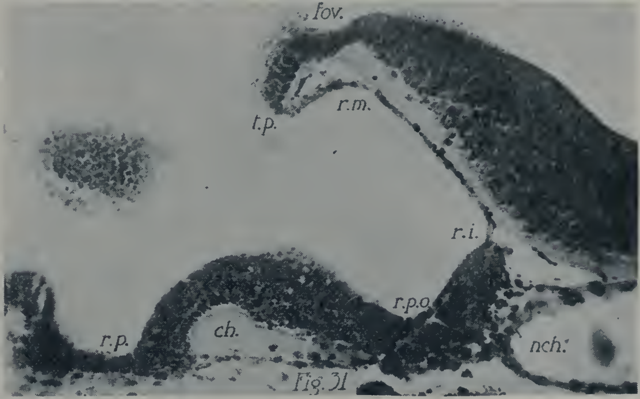


Fig.31

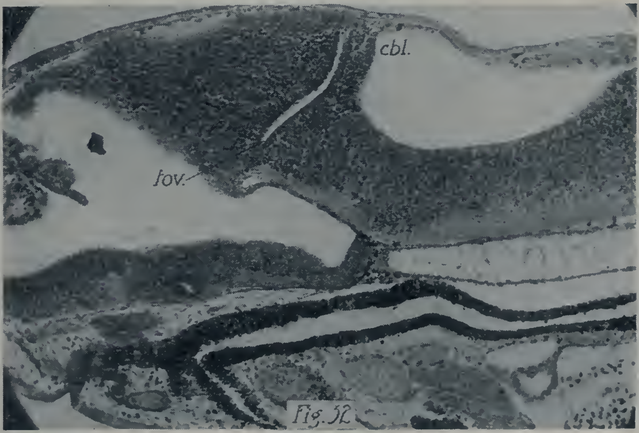


Fig.32

Fig. 30 Sagittal section of an older embryo of Amblystoma tigrinum to show the columnar pigmented cells of the anterior end of the floor plate. × 110.

Fig. 31 Sagittal section of a still older embryo of Amblystoma tigrinum when the fovea isthmi is well established. The recessus postopticus and recessus infundibuli are quite distinct. × 110.

Fig. 32 Sagittal section of an advanced embryo of Amblystoma tigrinum to show the position of the anterior end of the notochord and the lateral sulcus in the mesencephalon connected with the fovea isthmi. × 46.

Neal, H. V. 1898 The segmentation of the nervous system in Squalus acanthias. Bulletin of the Museum of Comparative Zoology, vol. 31, no. 7.

1914 The morphology of the eye-muscle nerves. Jour. Morph., vol. 25.

1918 The history of the eye muscles. Jour. Morph., vol. 30.

1919 Neuromeres and metameres. Jour. Morph., vol. 31.

Smith, G. Elliot 1908 The cerebral cortex in Lepidosiren. Anat. Anz., Bd. 33.

1910 The Arris and Gale lectures. The Lancet, Jan. 1, 15, and 22.

1919 A preliminary note on the morphology of the corpus striatum and the origin of the neopallium. Jour. of Anat., vol. 53.

Schulte and Tilney 1915 Development of the neuraxis in the domestic cat to the stage of twenty-one somites. Annals of the New York Academy of Sciences, vol. 24, pp. 319–346.

Stockard, Charles R. 1913 An experimental study of the position of the optic anlage in Amblystoma punctatum, with a discussion of certain eye defects. Am. Jour. Anat., vol. 15.

Stone, L. S. 1922 Experiments on the development of the cranial ganglia and the lateral line sense organs in Amblystoma punctatum. Jour. Exp. Zool., vol. 35.

AUTHOR'S ABSTRACT OF THIS PAPER ISSUED
BY THE BIBLIOGRAPHIC SERVICE, JULY 3

Reprinted from THE AMERICAN JOURNAL OF
ANATOMY, Vol. 31, No. 1, September, 1922

CHANGES IN THE MAMMARY GLAND OF THE ALBINO RAT (MUS NORVEGICUS ALBINUS) DURING LACTATION AND INVOLUTION

LEROY M. A. MAEDER

Institute of Anatomy, University of Minnesota, Minneapolis

TEN FIGURES

INTRODUCTION

The primary object of this study is to determine the anatomical changes which take place in the mammary gland of the albino rat during lactation and involution. In addition to extending our knowledge of the mammary gland in general, it is desirable to establish for this animal a norm which may serve as a basis for experimental work. A review of the literature shows that there has been very little work done on any one animal form in the nature of a detailed study of a complete series of stages during lactation and involution. Hence it was deemed desirable to work out these stages in the albino rat and thereby complete the series of studies on the life-cycle of the mammary gland in this animal begun by Myers ('16). Myers studied the earlier stages of the development of the mammary gland up to ten weeks of age, and Roberts ('21) continued the study up to the end of pregnancy. A preliminary report on the results of this investigation has been included in a previous article by the writer (Maeder, '21).

A review of the extensive literature on the mammary gland in various species and a histological study of the gland during lactation in the albino rat indicate that very slight changes take place during this period. Roberts' ('21) description of the gland at the close of pregnancy in most respects applies quite well to the gland during all stages of lactation. For the period of involution of the mammary gland, however, literature is less extensive, and apparently but little detailed work has been done upon this phase

TABLE 1

Series of animals during lactation

RAT NO.	AGE	GROSS BODY WEIGHT	NOSE-ANUS LENGTH	TAIL LENGTH	DAYS OF LACTATION
	days	*grams*	*mm.*	*mm.*	
M 1.1	112	125.0	160	143	0[1]
M 2.1	174	153.4	172	150	3.5
M 3.1	210	153.0	175	160	6.0
M 4.1	114	112.0	153	150	7.0
M 5.1	153	133.0	170	158	9.0
M 6.1	(?)	181.0	191	140	10.0
M 28.1	(?)	199.5	184	160	14.0
M 7.1	133	131.5	160	155	14.5
M 3.2	163	140.0	165	150	15.0
M 3.3	144	106.5	162	150	17.0
M 7.2	126	142.0	173	153	21.0
M 3.4	148	107.5	167	150	21.0

[1] Had just given birth to a litter, which had not nursed.

TABLE 2

Series of animals during involution

RAT NO.	AGE	GROSS BODY WEIGHT	NOSE-ANUS LENGTH	TAIL LENGTH	TIME SINCE NURSING
	days	*grams*	*mm.*	*mm.*	
M 8.1	(?)	253.0	199	193	24 hours
M 9.1	(?)	174.5	181		44 hours
M 10.1	176	157.5	184	153	47 hours
M 11.1	(?)	264.5	207	185	3 days
M 12.1	248	186.2	190	151	3 days
M 10.2	183	150.5	182	160	4 days
M 13.1	(?)	224.5	197	152	5 days
M 10.3	190	189.9	190	173	6 days
M 14.1	170	165.7	177	154	8 days
M 15.1	(?)	190.5	188		9 days
M 16.1	173	229.4	200	169	13 days
M 17.1	(?)	255.1	212	177	16 days
M 18.1	208	154.0	182	156	22 days
M 19.1	189	149.8	177	143	28 days
M 20.1	213	145.8	179	152	3 months
M 21.1	221	153.2	179	148	3 months

TABLE 3

Series of virgin animals

RAT NO.	AGE	GROSS BODY WEIGHT	NOSE-ANUS LENGTH	TAIL LENGTH
	days	*grams*	*mm.*	*mm.*
M 16.2	179	150.9	183	151
M 26.1	135	196.1	189	159
M 27.1	123	139.6	173	138

of the cycle. Most statements concerning the gland during involution are very general or incidental in character. No specific data as to how involution takes place or when it is complete were found among the earlier writings. A few of the more recent investigators have considered the subject in somewhat greater detail. Their work will be referred to later in the discussion of my findings.

This investigation, like those of Myers and Roberts, was conducted in the Department of Anatomy of the University of Minnesota. The writer gratefully acknowledges his indebtedness to Dr. C. M. Jackson for the constant aid, advice, and criticism during the course of this study. He is also thankful to Dr. E. T. Bell and Dr. J. A. Myers for many helpful suggestions in this connection.

MATERIAL AND METHODS

The material for this investigation consists in a series of twenty-eight primiparous and three virgin albino rats (Mus norvegicus albinus) from the colony in the Institute of Anatomy. The stages were selected as presented in the following tables (1, 2 and 3). In the first column the number for each rat is given. The letter indicates the series, the number preceding the decimal point is for the litter, and the number following designates the individual rat.

The animals were killed by ether and immediately weighed and measured, the data being given in tables 1 and 2. A longitudinal incision in the dorsal midline from the tip of the nose to the root of the tail was then made quickly with a scissors. Working laterally from this incision on either side, the integument with the mammary glands attached was carefully removed by dissecting with a sharp safety-razor blade along the fascial plane between the glands and the underlying muscle. In this way the whole skin with the mammary glands still intact in their normal position was secured.

The stages in lactation were used for cleared total mounts as well as for histological preparations. A modification of the method employed by Myers ('16) was found to be more suitable for the gland at this stage. The whole integument after removal was placed flat upon a cork sheet with the glandular surface up and held in position by small wooden pegs. The whole preparation was then fixed in Zenker's solution for twenty-four hours, washed for twenty-four hours in running water, and then carried up through the various grades of alcohol to 80 per cent. Appropriate pieces for histological sections were removed from selected areas. At this point the specimen for the final cleared preparation (total mount) was secured. Starting at one edge, the tela subcutanea was split from the corium, and this process continued over the entire area of the integument, using a sharp safety-razor blade to accomplish the separation. Thus a very thin fascial envelope containing the glandular tissue was obtained. This envelope was then dehydrated, carried through xylol into beechwood creosote, mounted upon a glass frame, placed in a thin specimen jar of appropriate size, and covered with beechwood creosote. Staining was found to be unnecessary, for after several weeks in beechwood creosote the darker glandular tissue could be seen in bold relief against the relatively transparent fascial envelope.

Only histological preparations were made from the stages of involution, as cleared preparations of a similar series were studied by Myers and Myers ('21). The skin with the glands was removed (as above), laid flat upon the table, and the inguinal and abdominal glands removed in toto from each side by lifting gently upon the gland with fine forceps and cutting with sharp pointed scissors the tela subcutanea between the gland and the corium. Tangential and transverse sections were then cut from these glands and placed in fixing fluids.

As fixatives, Zenker's solution, 10 per cent formalin, and Flemming's strong osmic-chromic acid solution were used. Paraffin sections were cut at 5μ. Sections of Zenker's fixation were stained with hematoxylin and eosin, cresyl violet, Mallory's connective-tissue stain, Unna's orcein, and Heidenhain's iron-alum hematoxylin, with and without counterstain of acid fuchsin. Sections of Flemming's fixation were mounted both without stain and with Heidenhain's iron-alum hematoxylin stain. Sections of formalin fixation were cut as frozen sections and stained both with hematoxylin and eosin and with sudan III for fat (by courtesy of the Department of Pathology). Bell's ('14) method, a combination of the techniques of Dietrich and Ciaccio, for differentiating between neutral fats and lipoids was tried, but was found to be unsatisfactory for mammary gland fat.

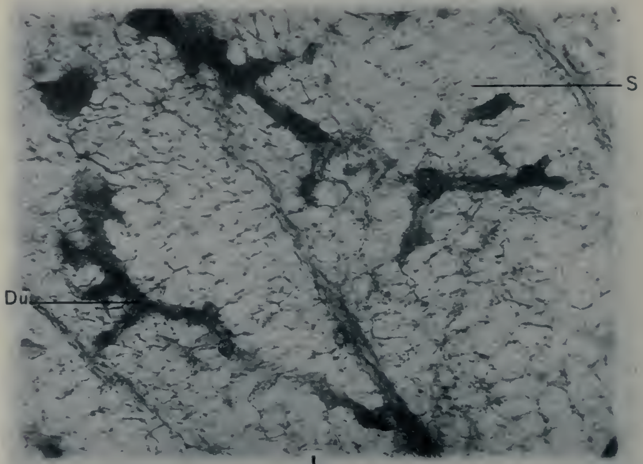
OBSERVATIONS

A. Gross changes

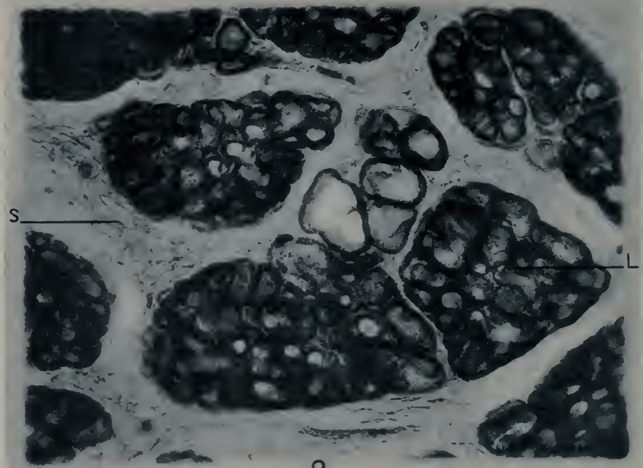
The nipple during lactation is long and prominent and can easily be drawn out to more than double its usual length. The hairs about the base of the nipple for a distance of about 2 mm. have been worn away, and thus appears what might be termed the areola of the nipple. After weaning, the nipples become progressively smaller in size and less prominent, and by the end of two weeks they reach a length about double that of the virginal nipple. The hairs have again begun to grow in about the base of the nipple. The nipple probably does not undergo any appreciable decrease in size after this time, for in most nonvirginal rats the nipple is apparently about twice as long as that of a virgin.

In the recently killed animal during lactation, the mammary glands are seen as well-defined masses, elevated above the surface of the rest of the skin. In the stages of involution, after two weeks, the glands are much smaller and less clearly outlined.

Cleared preparations (total mounts) of the glands in lactation showed that the macroscopic aspect of the gland remains unchanged throughout lactation and is the same as at the end of pregnancy. The glandular tissue appears as two dark V-shaped masses in the thoracic and inguinal regions. The apex of the first V lies slightly cephalad to, or at the level of, the fore limbs and is formed by the median overlapping of the glandular tissue of the first pair of thoracic glands. From this apex the mammary masses extend laterocaudad, being formed on each side by the overlapping of the first, second, and third thoracic glands, and lying along the medial aspect of the forelimbs. The caudal ends of these masses do not quite reach those of the second V.



1



2

Figures 1 to 5, inclusive, are microphotographs of frozen sections fixed in formalin and stained with hematoxylin and eosin. The unit of magnification for these first five figures is 60 diameters. Figures 6 to 10, inclusive, are drawings made with the aid of the camera lucida. Figure 6 is a drawing of a frozen section stained with sudan III. The remaining material was fixed in Zenker's solution, embedded in paraffin and stained with cresyl violet. All the figures are produced from transverse sections of portions of the gland from the abdominal-inguinal region.

Figures 1 to 5 show the general appearance of the gland in full lactation and up to eight days after weaning as compared to the resting virginal gland.

Figure 6 gives the disposition of fat in the stroma, epithelium and lumina.

Figures 7 to 10 show the finer details of structure of the gland during lactation and involution.

The apex of the second V lies slightly cephalad to the urethral orifice and is formed by the median overlapping of the second pair of inguinal glands. From this apex the mammary masses extend laterocephalad, being formed on each side by the abdominal, and first and second inguinal glands, and lying along the medial aspect of the hind limbs. Owing to the great engorgement of the glands with secretion and the overlapping of the glandular tissue, the individual ducts and lobules could not be made out (in gross preparations) except at the periphery.

B. Histology during lactation

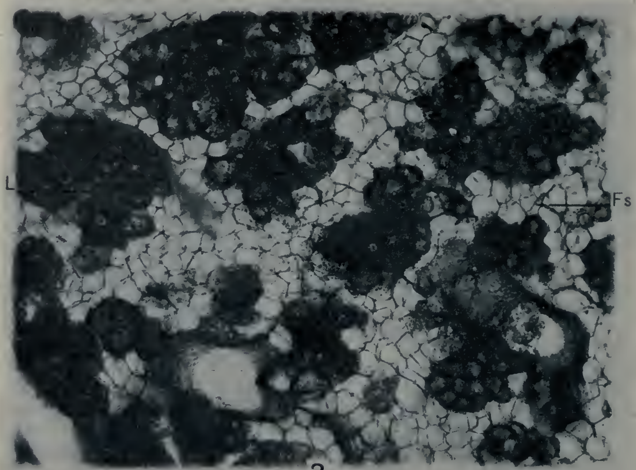
In general, any stage of the series of glands in lactation may be taken to represent the characteristic appearance of the gland during this period and at the end of pregnancy. Variations occur, however, both in different individuals and in different parts of the gland. The appearances also vary somewhat according to the technique used.

A frozen section of a gland at ten days' lactation, with hematoxylin-eosin stain (fig. 2), shows the general structure very well. This type of preparation shows most satisfactorily the relative proportion between parenchyma and stroma, the relative size and condition of the different lobules, and the position and relations of the ducts and the blood-vessels.

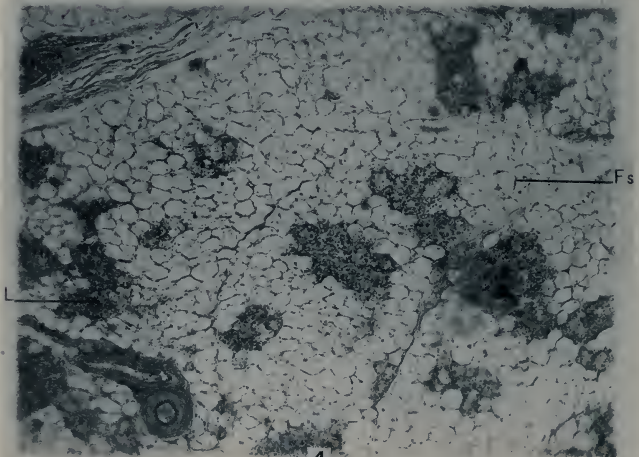
Paraffin sections stained with hematoxylin and eosin present much the same picture as the frozen sections. Being thinner, they make possible the study of histological details under greater magnification, but do not bring out quite so well the grosser architecture of the gland.

Fig. 1 Transverse section of the mammary gland of an adult virginal rat (M 27.1). Section about 25 μ thick; frozen section stained with hematoxylin and eosin. × 60. The parenchyma consists only of a few ducts, *Du*, ramifying through the fatty connective-tissue stroma, *S*. Figure 10 of the gland twenty-eight days after weaning gives a high-power view of a similar duct.

Fig. 2 Transverse section of the mammary gland of a rat (M 6.1) in the tenth day of lactation. Section about 25 μ thick; frozen section stained with hematoxylin and eosin. × 60. The parenchyma consists of definite, large lobules, *L*, with widely distended acini; the stroma has been reduced to thin connective-tissue septa, *S*. Figure 6 is a fat stain of another gland in lactation. Figure 7 gives a view of the more detailed structure in a similar stage.



3



4

Fig. 3 Transverse section of the mammary gland of a rat (M 12.1) three days after weaning. Section about 25 μ thick; frozen section stained with hematoxylin and eosin. × 60. The lobules, *L*, are smaller and the amount of fatty stroma, *Fs*, has increased proportionally. Figure 8 shows the same stage under high magnification.

Fig. 4 Transverse section of the mammary gland of a rat (M 13.1) five days after weaning. Section about 25 μ thick; frozen section stained with hematoxylin and eosin. × 60. The parenchyma is still further reduced in amount, the lobules, L, being smaller than in the three-day stage and the amount of fatty stroma, *Fs*, still further increased in amount.

Frozen sections of the fourteen-day stage, stained with sudan III (fig. 6), present the same general picture as similar sections stained with hematoxylin and eosin. In addition, they bring out more clearly the fat-cells in the stroma and also show the presence of fat-droplets in the lumina of the acini and the ducts and in the epithelium of both ducts and acini.

Flemming's osmic-mixture was also used, followed by paraffin sections at various stages in lactation. They show less clearly the general structure of the gland, since only the periphery is well penetrated by the osmic acid. The fat is well stained by this fixation. In the lumina and epithelium it usually appears in small spherical droplets. Here and there the lumen of an acinus remains filled with an almost completely black mass formed by the fusion of fat droplets. The fat cells of the stroma, however, appear as larger and more irregularly shaped structures.

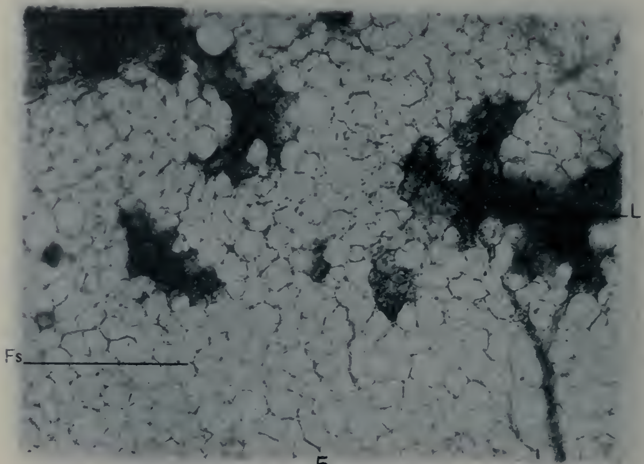
Heidenhain's iron-hematoxylin stains of paraffin sections show the nuclear structure most clearly.

The cresyl-violet staining of paraffin sections is of considerable value. This gives a very clear picture, sharply marking off the parenchyma from the stroma. It differentiates the mast cells and brings out clearly the cytological details. The connective tissue and the alveolar contents, however, do not take the stain well.

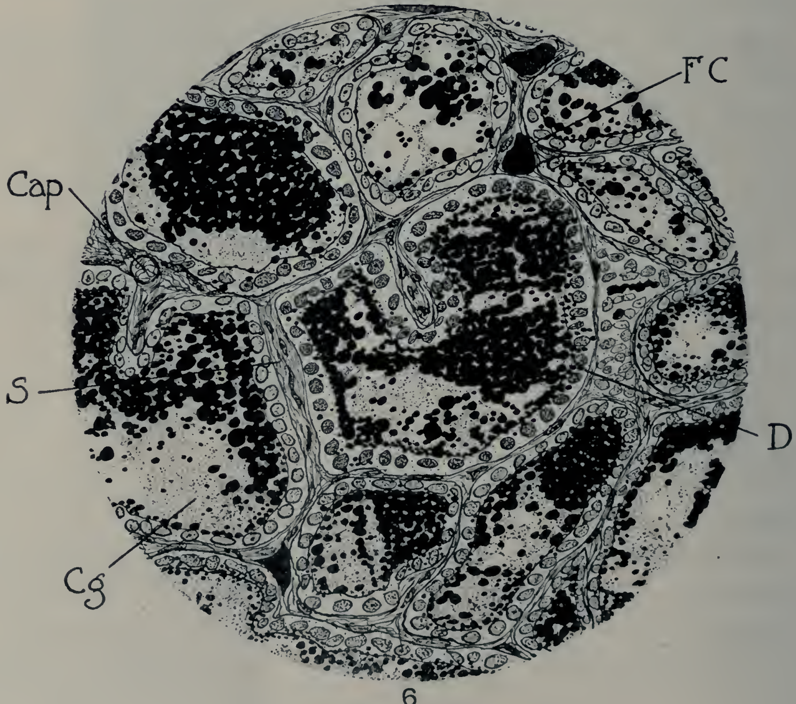
Mallory's connective-tissue stain with paraffin sections brings out distinctly the grouping of the glandular epithelium into lobules and reveals the septa of collaginous fibrous connective tissue between them.

Unna's orcein stain demonstrates the presence of elastic tissue fibers in the septa. The ducts are sharply marked out in these sections by the very definite surrounding sheath of elastic tissue fibers. The acini are also demarcated by the very fine septa and fibrillae prolonged out into the interacinous spaces.

The general arrangement and proportions of parenchyma to stroma (figs. 2 and 7) are seen to be practically the same in all sections at any stage of lactation and at the end of pregnancy. The glandular parenchyma is in great preponderance, being distributed in the form of definite, closely packed lobules which



5



6

reduce the stroma between them to relatively thin septa. The distention of the ducts and acini with secretion is fairly uniform. Dilated blood-vessels are quite numerous in the connective-tissue septa, while between many of the acini are seen small, widely dilated capillaries.

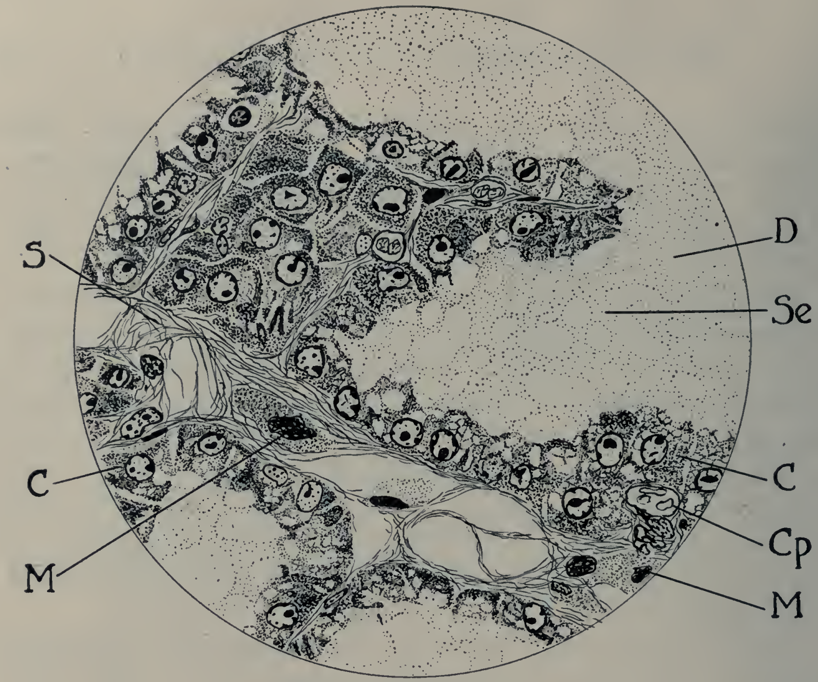
The lobules all present about the same general appearance, except for a narrow zone of glandular tissue about the periphery of the section. This zone presents smaller lobules with less widely distended acini which are composed of taller cells, take a deeper bluish stain (with hematoxylin) and contain little or no secretion. This zone is present in whole or in part in all sections, although in a few sections it is only suggested by a few such lobules at the periphery of the section. More frequently it is found partially or wholly surrounding a cross-section passing through the gland.

A small lymph-node is frequently noted in sections of the series (from the abdominal region). It appears as a small, well-circumscribed mass of lymphoid tissue, well embedded in the gland and surrounded by a thin, compact connective-tissue capsule.

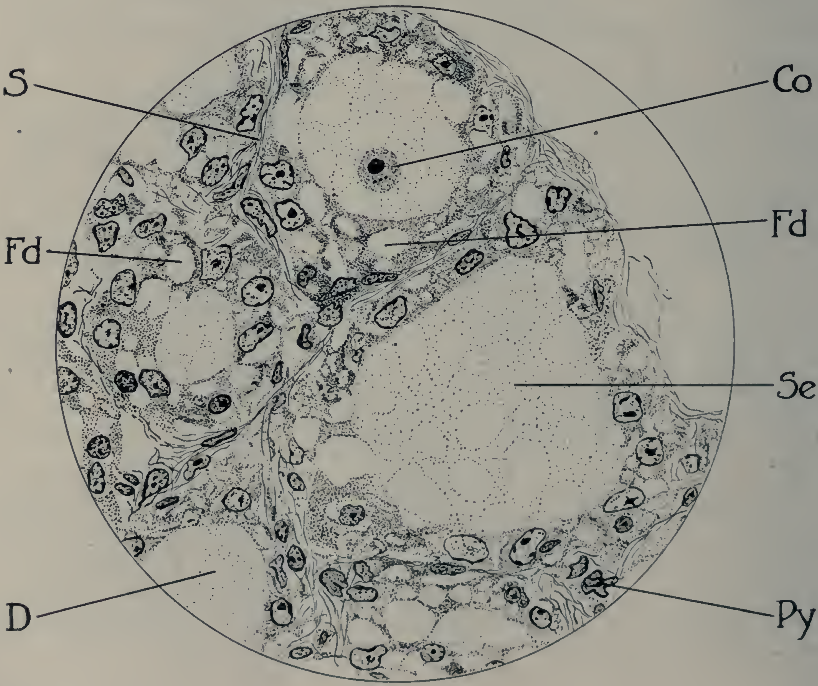
A study of the various sections under high power reveals many details of structure. The ducts are recognized by the more dense connective-tissue sheath which surrounds them and in many instances by the direct communication between them and adjacent lobules (fig. 2). They are also usually distinguishable from

Fig. 5 Transverse section of the mammary gland of a rat (M 14.1) eight days after weaning. Section about 25 μ thick; frozen section stained with hematoxylin and eosin. × 60. The parenchyma has again reached the stage similar to that of the resting gland, being composed chiefly of ducts. Parts of this section, however, show definite lobules resembling the lobules of the five-day stage in size (variability). Figure 9 is a high-power view of a section of the same gland.

Fig. 6 Portion of transverse section of the mammary gland of a rat (M 28.1) in the fourteenth day of lactation. Section about 25 μ thick; frozen section stained with sudan III. × 77. The fat is deposited as fat-cells, *F.C.*, in the stroma, *S*, and as droplets, *D*, in the epithelium and lumina. *Cap* designates a small capillary in the stroma and *Cg* the protein coagulum in the lumina of the acini. Figure 2 is a section of a similar stage stained with hematoxylin and eosin. Figure 7 is a drawing of a similar stage under high power.



7

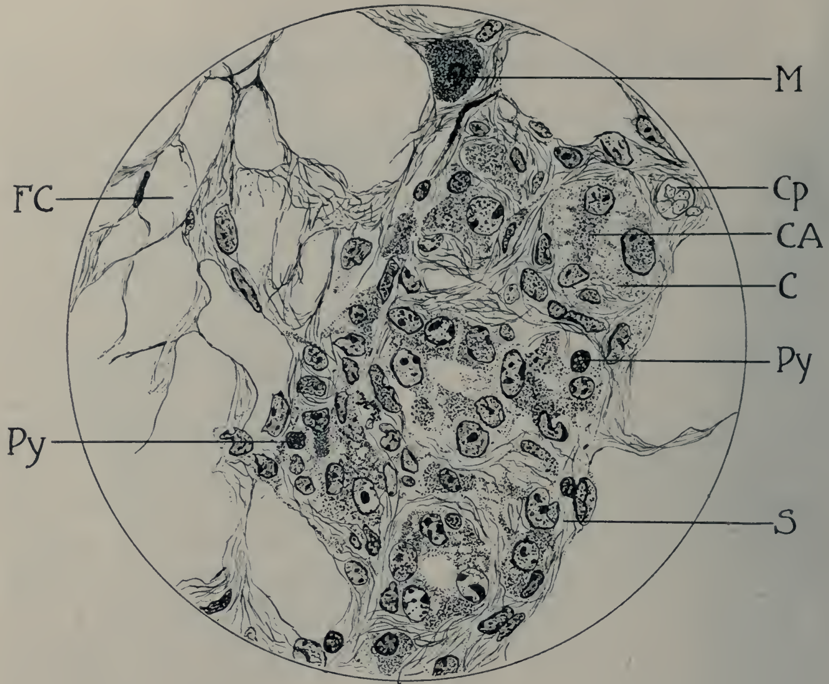


8

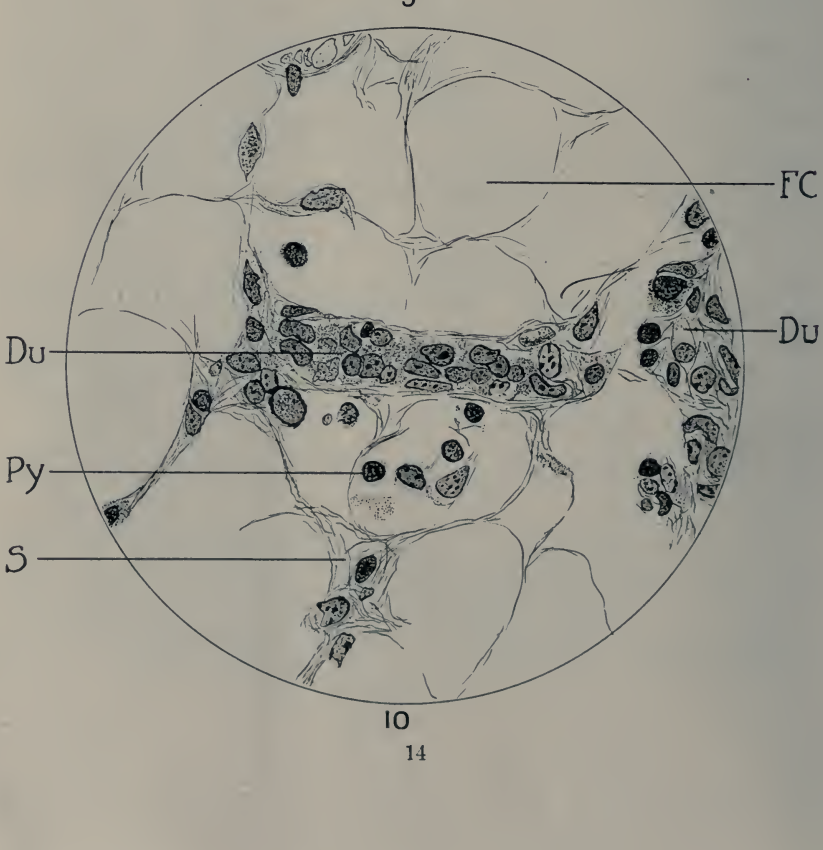
the neighboring acini by the fact that if their epithelium is of the same height as that of the acini their lumina are much larger, while if their lumina are of the same size as those of the acini their epithelium is usually taller. A careful study of all sections shows that the epithelium of the duct during lactation is of a single layer, regardless of the size or degree of distention. Cell boundaries are not demonstrable in the distended ducts and appear only indistinctly in the ducts with columnar epithelium. The cytoplasm shows no details of importance. The nucleus-plasma ratio would apparently be relatively high. The nuclei appear relatively large and vesicular, with definite outlines. The chromatin is mostly massed in one or two small clumps near the center, giving the appearance of nucleoli, or clinging in smaller masses to the nuclear membrane. In a few nuclei the chromatin is distributed more diffusely, giving the whole nucleus a dark appearance. Occasionally a small, round, rather dense nucleus, suggesting a lymphocyte, is found (fig. 7). Mitosis was observed only once in a cell of the epithelium lining the ducts. The lumina appear more or less distended with milk, showing a hemogeneous eosinophile (protein?) substance in which are numerous spherical droplets of fat (as demonstrated by osmic acid and sudan III). While fat droplets and granules are found in the lining epithelial cells, in general the ducts seem to show less secretory activity than do the acini.

Fig. 7 Portion of transverse section of the mammary gland of a rat (M 3.2) in the fifteenth day of lactation. Section 5 μ thick; paraffin section stained with cresyl violet. × 720. The acini are widely distended with secretion, *Se*, in which are suspended fat-droplets, *D*, of various sizes. The cytoplasm, *C*, of the cells contains deeply staining granules and secretory granules. The nuclei are spherical and contain clumps of chromatin. The connective-tissue stroma, *S*, is reduced to fine septa. Several mast cells, *M*, are shown. *Cp* designates several blood corpuscles in a small capillary. Figure 2 and 6 are of similar stages, but from different rats.

Fig. 8 Portion of transverse section of the mammary gland of a rat (M 11.1) three days after weaning. Paraffin section 5 μ thick, stained with cresyl violet. × 720. Definite signs of atrophy are evidenced by the presence of larger fat-droplets, *Fd*, and irregular and pycnotic nuclei, *Py*. A colostrum corpuscle, *Co*, is shown in one of the alveoli. The cytoplasm is more irregularly vacuolated and stains less deeply. Figure 3 is a low-power view of a similar stage.



9



10

The acini usually appear round and well distended, although there are variations in size and form (fig. 7). As compared with that of the ducts, the epithelium of the acini is flatter, more granular, and more vacuolated. It presents a quite uneven border on the side of the lumen, due to the greater number of fat-droplets in the various stages of secretion and discharge. Nothing suggesting the so-called 'decapitation' (detachment of the apex of the cell and its discharge into the lumen) was observed. The average number of cells in the circumference of an acinus is difficult to determine, but the number of nuclei seen in a section of an acinus apparently averages between fifteen and twenty.

The acini in portions of the gland exhibiting the greatest amount of secretory activity are characterized by: 1) the large vesicular nuclei with the chromatin distributed in small clumps; 2) uneven, indistinct cell boundaries on the side of the lumen; 3) highly granular and vacuolated cytoplasm, and, 4) distention of the acini with secretion containing numerous droplets of fat.

Mast cells are relatively numerous (fig. 7) and appear to be distributed quite evenly throughout the connective tissue stroma, as demonstrated by the cresyl-violet stain. They are relatively large in size, with deeply stained nuclei and coarse, purplish, granular cytoplasm.

Nothing suggesting a membrana propria was observed in the sections with the various methods of preparation.

Fig. 9 Portion of transverse section of the mammary gland of a rat (M 14.1) eight days after weaning. Paraffin section 5 μ thick, stained with cresyl violet. × 720. Remains of collapsed alveoli, *C. A.*, filled with degenerated, vacuolated cytoplasm. Pycnotic nuclei, *Py*, are quite numerous. The fat-cells, *F.C.*, have replaced the glandular parenchyma. A mast cell, *M*, is present. Figure 5 is the corresponding low-power view.

Fig. 10 Portion of transverse section of the mammary gland of a rat (M 19.1) twenty-eight days after weaning. Paraffin section 5 μ thick, stained with cresyl violet. × 720. Of the parenchyma there remains only ducts, *Du*, composed chiefly of closely packed, deeply staining cells in a syncytial mass of cytoplasm. A few atrophic cells, with pycnotic nuclei, *Py*, are found in the neighborhood of the ducts. The fat cells, *F.C.*, of the stroma have almost entirely replaced the parenchyma. Figure 1 corresponds well to a low-power view of a section at this stage.

C. Histology during involution

The various stages up to three months after weaning will be successively considered.

Twenty-four to forty-eight hours after weaning. Stained sections of the gland present practically the same appearance as during lactation. The parenchyma and stroma bear the same relative proportion to each other. The acini are widely distended with secretion and the epithelium still shows apparent secretory activity. In general, the ducts appear somewhat more widely distended with homogeneous contents than during the period of lactation. The characteristic peripheral zone of the gland is still present during this time.

Three-day stage (figs. 3 and 8). The parenchyma now appears somewhat reduced in proportion to stroma, in comparison with the preceding stage. This is shown by comparison in all sections of these stages, especially the frozen sections. The glandular substance appears more definitely grouped into small masses or lobules (fig. 3). The number of distended alveoli is markedly decreased with a progressive increase in the number of collapsed alveoli. Secretory activity, however, appears still quite well marked in many alveoli throughout the section. But in other alveoli definite signs of cessation of secretory activity and beginning atrophy are already evident. Such an area presents a characteristic appearance (fig. 8). The alveoli are smaller and contain little or no secretion. Large droplets of fat are frequently seen in the acinar cells, reaching to the very base of the epithelial cells, and in some cases crowding and deforming the nuclei. The cytoplasm appears more granular and stains less deeply. Many of the nuclei are somewhat irregular in outline and are hyperchromatic, taking a deeper stain. A few nuclei have become pycnotic.

Four-day stage. Stroma and parenchyma in sections now appear about equal in amount. The ducts as a rule are still well distended. They now appear more prominent in the section, owing to the absolute decrease in the number of alveoli. The relative number of distended alveoli seems greater than in the three-day stage (perhaps an individual variation). Secretory activity is still evident in some places; but beginning atrophy, as described in the preceding stage, is almost universal. The nuclei in general have lost their vesicular appearance and now appear more irregular in outline and stain deeply (hyperchromatic). Pycnosis is more frequent.

Five-day stage (fig. 4). Frozen sections of this stage show still more marked decrease in amount of glandular tissue, the glandular groups containing only a small number of alveoli and appearing as small islets in the fatty connective-tissue stroma. The glandular tissue is replaced by an increased amount of adipose tissue. The lumina of the acini and ducts are quite small and contain spherules of fat. Small fat-droplets are still seen in the epithelium of most acini.

Six-day stage. In this case the parenchyma greatly exceeds the stroma in amount, the condition closely resembling that found in the forty-four-hour stage. The secretory activity is very marked in the lactiferous epithelium. This apparently represents a marked individual variation, where for some reason the involution of the mammary gland has been delayed. The possible relation of such variations to the estrus cycle is mentioned later.

Eight-day stage (figs. 5 and 9). Here once more the stroma exceeds the parenchyma in amount. The glandular tissue is reduced to small cords with small lumina or no lumina at all. The glandular tissue, however, in most regions is still greater in amount than in the above-described five-day stage (probably an individual variation). Frozen sections stained with sudan III show that the small lumina of the ducts contain fat-droplets and that tiny fat-droplets are also present in the epithelium. True secretory activity is apparently absent (fig. 9). The cell-cords are evidently undergoing atrophy. The cell structure is indistinct; the cytoplasm seems to be reduced to a small amount of granular debris. The great majority of the nuclei are small, dark-staining, and irregular. Many nuclei appear pycnotic and some are broken up. The nuclear material is evidently being removed both by karyorrhexis and karyolysis. The nuclear substance greatly exceeds the cytoplasm in amount. Cresyl-violet stains show these conditions very clearly.

Nine-day stage. The gland has now reached a more advanced stage of involution, so that the structure here begins more nearly to resemble that of the resting adult virgin gland. A very few persistent acini are still present with atrophic epithelium, and a few of the smaller ducts still contain secretion within the lumen.

Thirteen, sixteen, twenty-two, and twenty-eight-day stages. The structure here closely resembles that of the virginal resting gland. Only a few ducts are seen passing through the stroma. These ducts now seem to possess a double layer of epithelium (which did not appear during lactation), with an inner layer of columnar and an outer layer of low epithelial cells. The cytoplasm is relatively more abundant; the nuclei are apparently smaller and less vesicular than in the lactating stages. They take a deeper stain and their chromatin is more evenly distributed. Each duct is surrounded by a connective-tissue sheath. No membrana propria is observed. The stroma is composed chiefly of adipose tissue through which the ducts pass. In some sections the adipose tissue seems to be arranged in lobules separated by fibrous connective-tissue septa.

Three months' stage. Sections of these stages present apparently the same structure as that of virginal resting glands. Apparently no further demonstrable changes have taken place at the end of three months, beyond those observed in the stage at thirteen days. Some cross-sections of the gland showed no glandular tissue whatever (probably depending upon the place from which the section was taken); other sections exhibited the same amount of glandular tissue as earlier stages (thirteen days and later); blood-vessels are apparently somewhat more numerous and run a more tortuous course than in the virginal gland.

DISCUSSION

A. Lactation

The significance of the so-called 'peripheral zone' of the mammary gland is difficult to determine. Its constant occurrence, either wholly or partly surrounding the section, would clearly indicate that it is not merely accidental. That it is an artefact and due to the manner of preparation appears improbable. Fixation or staining methods could hardly account for the small size of the lobules, the greater height of the epithelium, and the lack of contents in the lumina. The technique of embedding and sectioning likewise fails to account for it, since it appears not only in paraffin sections, but also in frozen sections of formalin material which are handled quite differently. Mechanical manipulation or pressure during preparation would scarcely produce a uniform diminution in the size of the alveoli. Such manipulation rather causes a general flattening of the alveoli, as shown in certain parts of a few sections which were accidentally subjected to local pressure with the forceps during removal of the gland. It would therefore appear that this peripheral zone has a definite morphological significance. Possibly it may represent a layer of incompletely developed, reserve alveoli, which have not been called into function by the demand upon the gland. Or it may represent a zone in which for some reason the nutritive conditions are less favorable than elsewhere. It may be recalled that other parenchymatous glands frequently present a peripheral zone of atrophic appearance.

The small lymph-node in the inguinal region was noted by Myers ('16) in the mammary gland of the albino rat. O'Donoghue ('12) found an analogous gland beneath the mammary gland of Dasyurus, and notes that its size varies somewhat with the activity of the mammary gland. This lymph gland could not be observed in my cleared total preparations, due to the opacity of the glandular tissue. Lymph-nodes associated with the mammary gland appear very distinctly in Myers' gross cleared preparations. In all cases a chain of two or three small nodes is found in the region of the abdominal gland. Since I always took the piece of of gland for histological preparation from the region of the abdominal and first inguinal glands, the frequent occurrence of this node in stained sections is easily understood.

A section of almost any stage of the lactating glands might represent the group. I have not been able to verify the observations of Kuramitsu and Loeb ('21) that the acini are not yet distended six to twelve hours after labor and that the maximum of secretory activity is not reached until about seven days after labor. There may be individual variation in this respect, however.

The epithelium in all ducts of my stages in lactation appears to be composed of a single layer of cells. Roberts ('21) shows in his figures a duct from a gland of a rat nineteen days pregnant, with two layers of epithelium. This would indicate that the transition from two layers to one layer takes place during the last days of pregnancy. As noted above, the two layers apparently reappear in the ducts toward the close of the period of involution.

A count of the nuclei in several acini indicates that the average number of cells in a section of each acinus lies between fifteen and twenty. Roberts ('21) found that the average number of cells about the lumen of the acini is eight, ranging from six to ten. This would indicate that the number of cells per acinus has increased in the latter part of pregnancy. But this is very doubtful, since cell division is rarely found at this time. It may be a matter of chance variation.

My results in general agree well with the now generally accepted view of the production of milk by a purely secretory activity of the glandular epithelium.

Colostrum corpuscles were not observed in any of my sections of the end of pregnancy stage or in any of the stages of lactation. Occasional cells resembling colostrum were found in stages after weaning (fig. 8). However, no special study of colostrum was made by me. There apparently is no evidence to show that the transition from the colostrum to pure milk secretion takes place after parturition in the rat. Roberts ('21) has described colostrum formation toward the latter end of pregnancy in the rat. Schil ('12) mentions a transitory or intermediate phase, lasting for five or six days after parturition in women, during which the colostrum becomes transformed and makes place for the normal milk secretion.

The mast cells are probably of no significance as regards lactation. Roberts ('21) found them in great numbers in the gland during pregnancy. They are also present in the virgin gland. It would therefore seem that they are present in the gland during the whole cycle.

B. Involution.

The relation of parenchyma to stroma remains nearly the same as during lactation for the first two days after weaning. After two days the parenchyma decreases in relative amount. It usually shows well-marked involution by the fifth day, and by the ninth day begins to approach its virginal resting condition. Variations, however, do occur, as evidenced by the fact that the glandular tissue in the eight-day stage was relatively greater in amount than in the five-day stage. Similarly, the six-day stage appeared scarcely different from the twenty-four-hour stage. These cases serve to illustrate the marked individual variability in the rapidity of involution in the mammary gland. Variability in different parts of the same gland was also noted. This variability of different parts of the same gland was noted in the rabbit by Schil ('12), who states that during the stages of lactation and involution the different lobules present variable aspects and that different acini are not in the same stage of secretion. Variability in different individuals and in different parts of the gland in the same individual is also characteristic of the human species (McFarland, '21).

Even in the resting mammary gland there may be considerable difference in the amount of parenchyma, as shown by Bouin and Ancel ('09) and Frank and Unger ('11) in the rabbit and by Sutter ('21) in the rat. These variations are ascribed chiefly to varying effect of the corpora lutea in different phases of the estrus cycle. It is quite possible that similar effects may likewise be responsible for some of the individual variations found in the mammary gland during the period of involution.

The secretory activity of the gland does not seem to be decreased before forty-eight hours after weaning. In the three-day stage secretory activity appears still quite marked in many alveoli, but in some alveoli secretory activity has evidently come to a standstill with the beginning of atrophy. The amount of secretory activity shows in general a progressive decrease in the four- and five-day stages. The six-day stage represents a marked variation, resembling very closely the forty-eight-hour stage.

The eight-day stage shows no secretory activity. This would indicate that secretory activity becomes greatly reduced after forty-eight hours and that by eight days it is usually absent altogether.

The lumina of the acini do not show any appreciable increased distention during the forty-eight hours after weaning. This is rather difficult to explain in view of the apparent continued secretory activity during this time. Possibly the products of secretion are absorbed as fast as they are produced. Moreover, in view of the fact that no actual measurements were taken and comparisons were made merely by inspection, it is quite possible that a slight increase in the diameter of the alveoli might not be perceptible. The findings of other investigators would make this seem quite probable. Schil ('12) states that for a few days after weaning in the rabbit the mammary gland still shows feeble secretion, the products accumulating in the alveoli and distending them. Berka ('11) also noted increased distention in the alveoli of the human mammary gland after weaning. Myers and Myers ('21) have also demonstrated an actual increase in size of the glands in gross cleared preparations after six hours and up to forty-eight hours.

The first signs of involution are found in the three-day stage, and become progressively more marked with each successive stage (excepting individual variations) until about the thirteenth day, when the gland again resembles the virgin resting gland very closely. Berka ('11) would consider the increased distention of alveoli immediately after weaning an early step in involution. It would probably be better to consider this phenomenon as a result of continued secretory activity of the gland; for it doubtless occurs many times during the course of normal lactation without being followed by actual involution, especially if the gland is not nursed frequently. Involution is apparently first evidenced by the occurrence, in the acinar epithelium, of larger fat-droplets which crowd the nuclei and deform them; also by a decrease in the size of the alveoli and a loss of the contents in their lumina. Duclert ('93) also noted large fat-droplets in the epithelium of glands in involution. There is no indication of the persistence of collapsed glandular acini, as claimed by Billroth ('87).

Nuclear changes seem to be very characteristic of the various stages of involution. They have also been described by Limon ('02) as undergoing changes with involution, especially as regards change in shape with a more diffuse distribution of the chromatin. Schil also describes nuclear degeneration (pycnosis and karyorrhexis). Duclert and Schil have mentioned the detachment of cells from the membrana propria and subsequent absorption.

Wahl ('15) found that during involution in the mammary gland of the rabbit the alveoli first shrink in size, then the alveolar cells degenerate and are absorbed, merely the ducts remaining as small groups of epithelial cells, with a small lumen or no lumen. Study of my sections has led to the conclusion that the disappearance of the acini is accomplished first by a simple atrophy of the cells, with shrinkage in the size of the cells and of the alveoli. With progressive atrophy of the cytoplasm, the nuclei become pycnotic, and finally (in most cases) the whole cell disintegrates and disappears.

Apparently during involution the contents of the lumina and ducts are removed by simple absorption, as found by Wahl in the rabbit. There is nothing to indicate that in the rat leucocytes have anything to do with the removal of the secretion, as found by Czerny ('90) and Mori ('92) in the human gland. Schil states that in rabbits the secreted milk transforms itself little by little into colostrum. No convincing evidence of such a process is found in the rat.

Great variability in the involution in the mammary gland has been observed by various investigators. Berka states that in the human mammary gland remains of lobules, groups of alveoli, may remain as evidence of faulty involution and that epithelial cells may long persist and contain fat after shrinkage of the lobules. Wahl found in the rabbit that different parts of the same gland undergo quite unequal retrograde metamorphosis and that alveoli in various stages of involution may persist for at least several months after lactation. These findings are in general agreement with my results; but the possibility of changes due to the estrus cycle (corpora lutea) must always be kept in mind. Wahl found that during involution in the rabbit the various arteries and veins of the gland appear for a short time tortuous and shrunken. He states that several characteristic differences between the virginal and involuted gland remain, the ducts remaining much longer and more ramified than in the virginal animal and that the number of veins and arteries supplying them is greater. This is in agreement with my findings in the rat, in which I find also the nipple maintaining a part of the hypertrophy which it undergoes during lactation.

SUMMARY

1. The macroscopic and microscopic structures of the mammary gland remain practically unchanged throughout the period of lactation in the albino rat.
2. Mitosis rarely occurs in the glandular epithelium during lactation, and was not observed in the stroma. Amitosis was not found.
3. The epithelium of the ducts of the mammary gland throughout lactation is single-layered.
4. The mammary gland possesses a fairly constant peripheral zone of characteristic structure throughout lactation and early involution. This is a somewhat atrophic or undeveloped zone of uncertain significance.
5. The mammary gland shows very little change during forty-eight hours after weaning. The alveoli probably tend to become somewhat more distended by the accumulation of secreted milk.
6. Secretory activity does not seem to be notably diminished before the third day after weaning. The cessation of secretion varies in different individuals and in different parts of the gland. Eight days after weaning no secretory activity is apparent.
7. A progressive relative increase in stroma and decrease in parenchyma takes place after the second day, the gland usually approaching the condition of the normal resting gland by the ninth day.
8. The removal of the epithelium of the acinus is accomplished by collapse of the acinus, and simple atrophy of the epithelium, followed by pycnosis and karyorrhexis or karyolysis. Large fat droplets frequently occur in the epithelial cells of the acini from the third to the fifth day of involution.

9. At the terminal stage of involution the structure of the mammary gland is very similar to that of the resting gland in the adult virgin.

10. The mammary gland is subject to considerable variability in rate and character of involution, either in different individuals or in different parts of the same gland. The former may be due in part to variation associated with the estrus cycle.

BIBLIOGRAPHY

Ancel, P., et Bouin, P. 1909 Sur la fonction du corps jaune. Action du corps jaune vrai sur la glande mammaire (troisième note préliminaire). Compt. rend. Soc. Biol., T. 66, p. 605.

Bell, E. T. 1914 On the differential staining of fats. Jour. of Path. and Bact., vol. 19, pp. 105–113.

Berka, F. 1914 Die Brustdrüse verschiedener Altersstufen und während der Schwangerschaft. Frankfurter Zeitschrift für Pathologie, Bd. 8, S. 203–256.

Billroth, Th. 1887 Diseases of the female mammary glands. Cyclopaedia of Obstetrics and Gynecology, vol. 9, pp. 1–158. Wm. Wood & Co., New York.

Czerny, A. 1890 Ueber die Brustdrüsensekretion beim Neugeborenen und über das Verhältnis der sogenannten Kolostrumkörperchen zur Milchsecretion. Sep. Abdr. aus d. "Festschr. zu E. Hennock's 70. Geburtstag." 34 p. (Cited by Schil.)

Duclert, L. 1893 Étude histologique de la sécrétion lactée. Thèse de Montpellier. 79 p. (Cited by Schil.)

Frank, R. T., and Unger, A. 1911 An experimental study of the causes which produce the growth of the mammary gland. Archives of Internal Medicine, vol. 7.

Kuramitsu, Choizu, and Loeb, Leo 1921 The effect of suckling and castration on the lactating mammary gland in rat and guinea-pig. Am. Jour. of Physiol., vol. 56, no. 1, pp. 40–59.

Limon, M. 1902 Phénomènes histologiques de la sécrétion lactée. Journal de l'anatomie et de la physiologie, T. 38, pp. 14–34.

McFarland, Joseph 1921 Preliminary remarks upon the functional variations of the normal human mammary gland. Proc. Amer. Assoc. Anat., Anat. Rec., vol. 21, no. 1, pp. 72–73.

Maeder, L. M. A. 1921 Clinical and experimental studies on lactation at the University of Minnesota. Arch. of Ped., vol. 28, no. 9, pp. 557–567.

Mori, A. 1892 Sulle variazioni di struttura della ghiandola mammaria durante la sua attivita. Sperimentale. Mem. orig., Firenze, vol. 46, pp. 444–456

Myers, Frank J., and Myers, J. A. 1921 Studies on the mammary gland. VIII. Gross changes in the mammary gland in the female albino rat during the period of involution. Proceedings Amer. Assoc. Anat., Anat. Rec., vol. 21, no. 1, p. 74.

Myers, J. A. 1916 Studies on the mammary gland. I. The growth and distribution of the milk-ducts and the development of the nipple in the albino rat from birth to ten weeks of age. Am. Jour. Anat., vol. 19, no. 3, pp. 353–389.

1917 Studies on the mammary gland. II. The fetal development of the mammary gland in the female albino rat. Am. Jour. Anat., vol. 22, no. 2, pp. 195–223.

1919 Studies on the mammary gland. IV. The histology of the mammary gland in male and female albino rats from birth to ten weeks of age. Am. Jour. Anat., vol. 25, no. 4, pp. 395–435.

1919 a Studies on the mammary gland. VI. The development of the mammary gland from its earliest appearance until the period of pregnancy. Am. Jour. of Diseases of Children. vol. 18, pp. 4–13.

O'Donoghue, C. H. 1912 Growth changes in the mammary apparatus of Dasyurus. Quar. Jour. of Micr. Science, vol. 57, pp. 187–234.

Roberts, F. L. 1921 Changes in the mammary gland of the albino rat during the second half of pregnancy. The Graduate School of the University of Minnesota; Papers from the Mayo Foundation for Medical Education and Research and the Medical School, vol. 1. W. B. Saunders Co., Philadelphia and London.

Schil, L. 1912 Recherches sur la glande mammaire, sur les phases qu'elle présente a cours de son évolution et leur determinisme. Thèse, Lyon.

Sutter, Monroe 1921 Cyclic changes in the mammary gland of the rat associated with the oestrous cycle. Proc. Amer. Assn. of Anatomists, Anat. Rec., vol. 27, p. 59.

Wahl, H. M. 1915 Development of the blood vessels of the mammary gland in the rabbit. Am. Jour. Anat., vol. 18, pp. 515–524.

10141

AUTHOR'S ABSTRACT OF THIS PAPER ISSUED
BY THE BIBLIOGRAPHIC SERVICE, MARCH 20

Reprinted from THE ANATOMICAL RECORD
Vol. 23, No. 3, March, 1922

EFFECTS OF VARIOUS TYPES OF INANITION UPON THE MITOCHONDRIA IN THE GASTROINTESTINAL EPITHELIUM AND IN THE PANCREAS OF THE ALBINO RAT

SHIRLEY P. MILLER

Institute of Anatomy, University of Minnesota

Although there is an extensive literature upon mitochondria, the most of this is of a purely morphological nature. But few investigations have been made to determine their modification in number, size, or shape under experimental or pathological conditions. The observations of Lewis' ('15) would indicate that mitochondria are very labile and variable in their morphology. Changes in mitochondria have been described by Homans ('15) in pancreatic islet cells during diabetes; by Scott ('16) in the pancreatic cells of white mice in phosphorus poisoning; by Goetsch ('16) in thyroid cells during goiter, and by Cowdry ('20) in plant rootlets subjected to various harmful conditions. McCann ('18) observed persistence of mitochondria in the nerve cells of monkeys dying of experimental poliomyelitis. Rasmussen ('19) was unable to find any appreciable decrease in the mitochondria in the nerve cells of hibernating woodchucks. Russo ('12) found an increase in the amount of mitochondria in the oöcytes of rabbits during lecithin feeding. Apparently the only published observations on the effects of inanition upon the mitochondria are the results briefly stated by Schun Ichi Ono ('20) at a meeting of the Anatomical and Anthropological Association of China. He demonstrated histological preparations showing the effect of starvation upon the mitochondria in the somatic cells of Ascaris, causing them to become granular. He also observed altered size and shape of mitochondria in the tissues of starved rodents. Since further investigation of this question seemed desirable, the present study was undertaken in order to determine the changes in the mitochondria of the gastro-intestinal epithelium and of the pancreas in the albino rat during various types of inanition. During the progress of this study, it seemed wise to have for comparison some material which had been submitted to other experimental conditions than types of starvation. Therefore, a number of rats were asphyxiated by suffocation.

MATERIAL AND METHODS

The thirty-four albino rats used in these experiments were all males except three. The age of the animals ranged from new-born to adult. Three animals were new-born, weighing 4 grams each. Two were mature adults with a weight of about 275 grams. The remainder were young adults weighing from 140 to 160 grams. All animals were weighed at the beginning and end of the experiments. The lengths of the body and the tail were taken at the time of death. The age of all animals was known. As far as possible, test animals and controls were from the same litter, and were killed at the same time. The animals subjected to starvation were killed in the advanced stages of inanition, most of them when the animal was near death.

The animals submitted to asphyxiation were placed on a glass plate and covered with a bell jar of about 1000 cc. capacity. The chamber was made air tight by means of vaselin spread around the juncture of plate and bell jar. Six to seven hours elapsed before the rats were asphyxiated.

The thirty-four rats were divided into the following groups: nine were given no food, but allowed water; one was given neither food nor water; one was a new-born and not allowed to nurse.

Through the kindness of Prof. J. F. McClendon, four rats were obtained which had been fed on diets deficient in water-soluble A vitamine in various degrees. I am likewise indebted to Prof. R. Adams Dutcher for two rats, one fed upon an exclusive diet of gelatin for thirty days and the other for the same length of time on an exclusive diet of zein. Seventeen normal rats were used as controls.

The tissues of both test rats and control animals were fixed in the same manner and simultaneously dehydrated and imbedded in paraffin.

Bensley's acetic-chromic-osmic and Regaud's formalin-bichromate fixers were used. Sections were cut 2 and 3μ thick, and mounted in a series of ten or twelve to a slide. In some cases test and control tissues were mounted on the same slide—a method which gave the same staining technique for each.

The sections were stained by the acid-fuchsin-methyl green method of Bensley.

OBSERVATIONS

At the outset it may be well to emphasize the great variation found in the form and number of mitochondria in both the test and control tissues, due in part to the difficulty in securing uniformity of technique. Not all the cells of the epithelium of the test animals exhibit the modifications which are described. There are areas in the epithelium in which the cells show evidence of necrosis as a result of injury due to experimental conditions. In such circumscribed regions mitochondrial changes in form and number were apparent, especially in the deeper portions of the mucosa.

The normal stomach. In the gastric glands the mitochondria of the chief cells are short, straight rods. In most of the cells one may also find spherical mitochondria, but only a few to a cell. The spherical forms present the appearance of having been separated from the rod-like forms. Occasionally there is a linear arrangement of such spheres, as if a whole rod had become segmented. The rods vary from 2 to 5μ in length and the spheres from five-tenths to eight-tenths of a micron in diameter. The mitochondria are in most cells uniformly distributed throughout the cytoplasm. In exceptional cases there is a peripheral condensation, or grouping of the mitochondria, chiefly at the base of the cell.

Because of the difficulty in distinguishing between the acidophile secretory granules and the mitochondria of the parietal cells, no special study was made of these cells. Satisfactory results in case of these cells could be obtained only by the use of the intra vitam stains. The cells of the foveolae and the surface epithelium have distinctly more mitochondria in them than do those of the glands. The mitochondria are uniformly distributed throughout these cells, and the size of the mitochondria is very nearly the same as of those in the chief cells.

The stomach of test rats. A study was made of the stomach in four rats fed for periods from 89 to 105 days on a diet variably deficient in water-soluble A vitamine. The chief cells of the gastric glands, in areas evidencing injury, exhibit changes in the mitochondria. This is especially true in case the diet is markedly deficient in the vitamine. The rod-like forms of mitochondria are entirely lacking, although a few spherical mitochondria occur. The cytoplasm of such cells exhibits a fine vacuolization at the periphery towards the lumen of the gland. Occasionally one finds this vacuolization throughout the cell. In the surface epithelium and the gastric foveolae the mitochondria show no well-marked or constant changes.

In the gastric glands of the two rats which had been fed on a diet of gelatin or zein, no mitochondria were found in the chief cells of the rather extensive necrotic areas.

Similarly in the rats subjected to acute inanition and in the last stages of starvation, no mitochondria occur in the chief cells of degenerated areas. Even in areas not exhibiting marked degeneration there are few if any mitochondria to be noted.

The cells of the foveolae and the surface epithelium, in all the experimental rats mentioned above, do not show as marked changes in the mitochondria. In those of the acute starvation series the rods are replaced to some degree by spheres. In but very few cases was it possible to find marked changes in the mitochondria of the cells of the foveolae and surface epithelium.

Observations upon the stomachs of asphyxiated rats show similar changes in the mitochondria of the chief cells, especially in areas evidencing injury. There are no rods, but spheres are present and apparently in reduced number. The cytoplasm of such cells is more or less vacuolated, resembling this condition in the cells of the other experimental animals. The cells of the foveolae and the surface epithelium show no changes in the mitochondria.

The normal duodenum and pancreas. In the normal rats the mitochondria in the cells of the glands of Lieberkühn of the duodenum resemble those of the chief cells of the stomach. They are somewhat shorter, however, measuring from 2 to 4μ in length. Their distribution in the cells is likewise similar to that of the chief cells of the stomach. The epithelial cells of the villi resemble those of the foveolae and surface cells of the stomach epithelium, in so far as the mitochondria are concerned.

The mitochondria of the pancreas cells appear as long, straight rods. Their length is about twice that of those in the chief cells of the stomach. They are uniformly distributed throughout the protoplasm in the vicinity of the nucleus. The protoplasm of the cells nearest the lumen of the pancreatic alveolus contains secretory granules more frequently than it does mitochondria.

In the rats fed upon a vitamine-deficient diet the gland cells of the duodenum show spherical more frequently than rod-like mitochondria. Very often both spheres and rods occur in the same cells, but the rods are always fewer in number.

In acute inanition the mitochondria are usually absent in the cells of the glands of Lieberkühn and in the villus epithelium they are apparently decreased in number.

In the asphyxiated material there is no appreciable change in the mitochondria in the cells of either the glands or the surface epithelium of the villi.

The pancreas of the experimental animals does not exhibit abnormal areas in which the cells show evidences of injury such as occur in the stomach and duodenum. In vitamine deficiency the mitochondria are present in the gland cells, but the number of rods is decreased, most of the mitochondria being spherical in form. In the pancreas of animals suffering from acute inanition no rods occur. All of the mitochondria appear spherical in shape. Asphyxiation does not appear to modify the mitochondria in shape or number.

Because of the minuteness of the mitochondria in the pancreatic islet cells, no special study of them was attempted in these cells.

CONCLUSIONS

Vitamine deficiency and acute starvation may produce changes in the mitochondria in the gastro-intestinal epithelial cells and in the gland cells of the pancreas. Asphyxiation apparently does not produce such marked changes.

The amount of injury to the cell must be rather severe in order to bring about such changes. Cowdry ('20) reached the same conclusion from experiments upon plant rootlets.

The changes observed may involve: 1) a transformation of mitochondria from rod-like to spherical forms; 2) an apparent reduction in number of the mitochondria; 3) or even the total disappearance of mitochondria from the cells.

Because of the difficulty in obtaining uniformity of technique and the extreme variations observed in the staining reactions even in the normal cells, it is evident that great caution should be observed in drawing conclusions as to the effect of environmental changes upon mitochondria.

LITERATURE CITED

Cowdry, N. H. 1920 Experimental studies on mitochondria in plant cells. Biol. Bull., vol. 39, p. 188.

Goetsch, Emil The functional significance of mitochondria in toxic thyroid adenoma. Johns Hopkins Hosp. Bull., vol. 27, pp. 129–133.

Homans, J. 1915 A study in experimental diabetes in the canine and its relations to human diabetes. Jour. Med. Research, vol. 33, pp. 1–51.

Lewis, M. and W. H. 1915 Mitochondria in tissue cultures. Am. Jour. Anat., vol. 17, pp. 399–401.

McCann, Gertrude A study of mitochondria in experimental poliomyelitis. Jour. Exp. Med., vol. 27, pp. 31–37.

Rasmussen, A. T. 1919 The mitochondria in nerve cells during hibernation and inanition in the woodchuck. Jour. Comp. Neur., vol. 31, pp. 37–49.

Russo, A. 1912 Aumento dei granuli protoplasmatici nell' oocite delle coniglie iniettate con lecitin, loro diminuzione nelle coniglie digiunanti e loro natura lipoide e mitochondriale. Arch. f. Zellforsch., Bd. 8, Heft 8, S. 203–216.

Schun, Ichi Ono 1920 Effect of starvation and refeeding upon the mitochondria and other cytoplasmic contents. Proceedings of Anat. and Anthrop. Ass. China.

Scott, J. M. 1916 Experimental mitochondrial changes in the pancreas in phosphorus poisoning. Am. Jour. Anat., vol. 20, pp. 237–253.

2015

THE DEVELOPMENTAL TOPOGRAPHY OF THE LARYNX, TRACHEA AND LUNGS IN THE FETUS, NEW-BORN, INFANT AND CHILD *

G. J. NOBACK, M.A., PH.D.
RICHMOND, VA.

The development of the respiratory system in the embryonic period of man has been carefully worked out by a number of observers and the features of the process are well known. On the other hand, the development of this system from the third fetal month to birth, in early infancy, later infancy and childhood has received little attention. The present report is a study of the topographic relationships of the larynx, trachea and lungs, with especial emphasis on the changes in this relationship during the entire developmental period. All the available data on the subject, for infancy, childhood and adult life, have been correlated with my findings in the fetus, the new-born infant and the child. It is hoped that in this way a picture may be sketched of the relation of the parts of the respiratory system to the vertebral column, beginning with early fetal life and ending with maturity.

A few observations in addition to those mentioned above have also been made and recorded. These include the lobation of the lungs, the development of the cardiac notch, the angle that each bronchus makes with the midsagittal plane and the relation of the apices of the lungs to the suprasternal notch. A study of the lineal growth of the component parts of the respiratory system was also made in conjunction with the present paper, but the results of that study will be reported separately.

MATERIAL AND METHODS OF COLLECTING DATA

The material used in this study consisted of 102 fetuses and full-term new-born children, ranging in crown-heel or total body length from 10 to 55 cm.; midsagittal sections of a 5 year and an 8 year old child; a model of the topography of the thoracic and abdominal viscera of a 65 mm. human embryo, and a series of tracings of medially sectioned human fetuses. The major part of the material forms part of the collection of the Institute of Anatomy of the University of Minnesota; the remainder is part of the collection of the Department of Anatomy of the Medical College of Virginia. Eighty-two of the fetuses were still-born and twenty-two were infants in whom respiration had been partially established, as indicated by the condition of the lungs. The fetuses and full-term infants were preserved by intravascular injection of an

---

* From the departments of anatomy of the University of Minnesota and of the Medical College of Virginia.

aqueous solution of 10 per cent. formaldehyd and 1 per cent. chromic acid. No material in which pathologic conditions were macroscopically observable was used in this study.

The material was prepared in the following manner:

The skin, muscles, etc., were dissected from the anterior of the neck and thorax; the clavicles and costal cartilages were cut along the anterior axillary line, and the anterior part of the thoracic cage was then removed. The infrahyoid muscles, thyroid gland, thymus, heart and great vessels were next carefully dissected out, leaving the larynx, trachea, bronchi and lungs fully exposed in situ. The chin was always held in a horizontal position in order to avoid elevation or depression of the larynx and trachea due to over-extension or depression of the head.

The thyrohyoid membrane was next cut in order to make visible the tip of the epiglottis, which was taken as the superior limit of the larynx. A pin was then inserted into the vertebral column to mark the level of the tip of the epiglottis. The inferior vertebral level of the larynx was marked by a pin at the level of the inferior margin of the cricoid cartilage. A pin was inserted into the vertebral column on each side at the apex of each lung in order to determine its uppermost level. Pins were similarly placed at the most inferior level of each lung. Later, when the heart was removed, the vertebral level of the tracheal bifurcation was marked by a pin inserted into the vertebral column.

The following observations were made and recorded from each individual:

1. Crown-heel length, or total body length, from the vertex of the head to the base of the heel.
2. Crown-rump length, or sitting height, from the vertex of the head to the tip of the coccyx.
3. Vertebral level of the tip of the epiglottis.
4. Vertebral level of the inferior margin of the cricoid cartilage.
5. Vertebral level of the bifurcation of the trachea.
6. Relation of the apices of the lungs to the suprasternal notch.
7. Vertebral level of the apex of the right lung.
8. Vertebral level of the apex of the left lung.
9. Vertebral level of the most inferior part of the inferior margin of the right lung.
10. Vertebral level of the most inferior part of the inferior margin of the left lung.
11. Angle formed by the right bronchus with the midsagittal line.
12. Angle formed by the left bronchus with the midsagittal line.
13. Number of lobes and irregularities of fissures in the right lung.
14. Number of lobes and irregularities of fissure in the left lung.
15. Greatest depth of the cardiac notch.

In order to determine the vertebral levels of the several structures and organs, the vertebral column was split in its midline and the levels of the insertions of the pins were observed and recorded.

THE LITERATURE

The changes in topography of different parts of the human respiratory system in the developmental period have received considerable attention from several investigators, although apparently all the levels here presented have not been considered together in any single study in the past. The relation between the trachea, lungs, thymus and heart in fetal life and in the new-born was discussed in a previous paper.[1] There are several illustrations in the literature of midsagittal sections of fetuses [2] and new-born infants,[3] from which the laryngeal levels may be obtained. All of these which I have found have been plotted against total body length as was done in my own cases. These are shown in Figure 4, along with the data in the literature for these levels obtainable for infancy,[4] childhood,[5] and adult life.[6]

---

1. Noback, G. J.: A Contribution to the Topographic Anatomy of the Thymus Gland, with Particular Reference to Its Changes at Birth and in the Period of the New-Born, Am. J. Dis. Child. **12:**120 (Aug.) 1921.

2. Ballantyne, J. W.: An Introduction to the Diseases of Infancy, Edinburgh, 1891, pp. 56-57. Cheivitz, J. H.: A Research on the Topographical Anatomy of the Full-Term Human Fetus in Situ, Copenhagen, 1899, pp. 14-16. Keibel and Mall: Human Embryology, Philadelphia, 1910, Vol. 2, p. 402, Mehnert, E.: Ueber Topographische Altersveränderungen des Atmungsapparats, Jena, 1901. Merkel, F.: Menschliche Embryonen verschiedenen Alters auf Medianschnitten untersucht, Göttingen, 1894. Scammon, R. E.: Private collection, University of Minnesota Department of Anatomy. Symington, J.: On the Relation of the Larynx and Trachea to the Vertebral Column in the Fetus and Child, Edinburgh M. J. **26:**913, 1881.

3. Birkenbusch: Die inneren Proportionen des menschlichen Halses in den verschiedenen Lebensaltern, Dissertation, Göttingen, 1890. Jackson, C. M.: On the Developmental Topography of the Thoracic and Abdominal Viscera, Anat. Rec. **3:**361, 1909. Merkel, F.: Handbuch der topographischen Anatomie, Braunschweig, 1899, Vol. 2, p. 405 (Fig. 70). Mettenheimer, H.: Ein Beitrag zur topographischen Anatomie der Brust Bauch und Beckenhöhle des neugeborenen Kindes., Morph. Arbeiten **3:**301, 1893. Piersol, G. A.: Human Anatomy, Philadelphia 1908, p. 1828. Ribemont, A.: Recherches sur l'anatomie topographique du fetus, 1878, Thèse, Paris, No. 203. Rudinger, F.: Topographisch-chirurgische Anatomie des menschen, Atlas, Stuttgart, 1873, Plate 4, Figure a.

4. Engel, St.: Form, Lage und Lageveränderungen des Bronchialbaumes im Kindesalter, Arch. f. Kinderh. (Festschrift f. Baginsky) **60-61:**267, 1913. Jackson, C. M.: Private collection, University of Minnesota Department of Anatomy. Symington, J.: The Topographical Anatomy of the Child, Edinburgh, 1887, (Plates 1 and 2).

5. Dwight, T.: Frozen Sections of a Child, New York, 1881, p. 15, Plate 3. Gedgowd, V. A.: Anatomical Peculiarities of the Respiratory Organs in Children, Dissertation, St. Petersburg, 1900, pp. 178, Plate 1 (Russian). Sluka, E.: Ueber Roentgenbefunde bei tuberculösen Kindern mit expiratorischen Keuchen, Wien. klin. Wchnschr. **23:**156, 1910. Zuckerkandl, E.: Atlas der topographischen Anatomie des Menschen, 1899, p. 163, Figure 170.

6. Corning, H. K.: Lehrbuch der topographischen Anatomie, Ed. 10 and 12, Munich and Wiesbaden, 1920, p. 202, Figure 164. Cunningham: Textbook of Anatomy, Ed. 4, 1913, p. 1077. Gray-Lewis: Anatomy of the Human Body, 1920, Philadelphia, p. 1084. Hyrtl, J.: Lehrbuch der Anatomie des Menschen,

(Footnote 6 continued on next page)

The most comprehensive study of the topographical changes of the human respiratory system is that of Mehnert (1901).[7] His study includes the literature on the subject up to that time, not only for fetal life but also for all stages through senility in postnatal life. The prenatal material which he personally studied was somewhat limited in that the epiglottis was not considered and that his cases of fetuses and new-born infants numbered only ten in addition to seven cases of Merkel and one case of Disse, or a total of eighteen. He considered the following levels: cricoid cartilage, tracheal bifurcation and the inferior margin of the lungs; all of which, with the addition of the epiglottis and the superior limit of the lungs in relation to the sternal notch and to the vertebral column, were also utilized in the present study.

Mehnert concludes that there is a definite descent with age, but states that the fetal cricoid level is similar to that in the new-born. He finds marked variation in the fetal levels of the cricoid and states that this level shows no marked tendency upward or downward but rather an oscillation. This, he believes, may be partly due to the varying position of the heads in the different cases studied, but he says that the differences in this level should be regarded as individual variations. The level of the inferior margin of the cricoid cartilage in the new-born also varies markedly according to the data of several other investigators and the one case of his own.

Mehnert's conclusions regarding the vertebral level of the tracheal bifurcation are similar to those regarding the level of the larynx. Here, again, he had ten cases of his own and seven cases of other investigators. He states that there are as great variations in this level in some fetal months as are found in his whole series, and that therefore the wide fluctuations should be regarded as individual variations. The level of the bifurcation in the trachea in the new-born he finds to be lower than that in the fetus. The explanation of this, he believes, lies in the fact that, in the fetus, the trachea is craniad to the viscera; whereas, in the new-born,

---

Wien, 1889. Joessel, J.: Lehrbuch der topographischen chirurgischen Anatomie, Bonn, Ed. 2, 1899. Luschka, H.: Die Anatomie der Brust des Menschen, Tübingen, 1863, p. 463. Morris-Jackson: Text-Book of Human Anatomy, Ed. 6, Philadelphia, 1921, p. 1254. Potter, Peter: Topography of the Thorax and Abdomen, University of Missouri Studies, Science Series, Vol. 1, No. 1, Columbia, Mo., 1905. Poirer et Charpey: Traité d'anatomie humaine, Paris, 1901, Vol. 3, p. 402 and Figure 203. Quain's Elements of Human Anatomy, London, 1914, Vol. 2, Part 2, p. 152. Rauber-Kopsch: Lehrbuch der Anatomie, Leipzig, 1911, Ed. 9, No. 4, p. 190. Spalteholz, W.: Atlas der Anatomie des Menschen, Leipzig, 1920, p. 480, Figure 516. Testut, L.: Traité d'anatomie humaine, Paris, 1911, Vol. 3, p. 763, Figure 676. Testut et Jacob: Traité d'anatomie topographique, Paris, 1909, p. 629. Toldt, C.: Anatomischer Atlas, Ed. 6, Vol. 4, p. 483, Figure 813.

[7] Mehnert: Footnote 2, fourth reference.

it is caudad, and therefore has the weight of the viscera pulling it downward.

According to Mehnert, the level of the larynx and of the tracheal bifurcation show no definite descent during prenatal life, but between early fetal life and maturity there is a descent in these levels of a distance represented by five vertebrae. The inferior margins of the lungs in this period of time also undergo a descent which he measures by two intercostal spaces.

Jackson,[8] in whose private collection are a number of drawings of midsagittal sections of specimens in the Leipsic Museum, furnishes levels of the epiglottis and larynx of the two new-born infants and of a 2-day-old child.

Merkel (1894)[9] illustrates and describes several embryos, fetuses, one new-born child, and an adult in midsagittal section. The levels of the epiglottis and cricoid in all of these were taken off and used in this study. Merkel believes that even though the trachea extends lower in the new-born than in the embryo, the relative increase in tracheal length is more apparent than real and that this is due to slackening in growth of the vertebrae in late fetal life.

Symington (1885)[10] states that, in the new-born, the larynx and trachea terminate at a higher level than in the adult, but he was unable to find any definite statement as to their precise position in relation to the vertebral column. He found the larynx terminating opposite the middle of the fourth cervical vertebra and the trachea at the level of the lower border of the second thoracic vertebra; and he records the levels of the upper and lower limits of the larynx and of the bifurcation of the trachea in fetuses of 4, 6 and 7 months.

Scammon,[11] in his collection, has drawings of midsagittal sections of fetuses of the following crown-rump measurements: 34.7 mm., 43.3 mm. and 26.8 mm. These measurements, as all other measurements given in the literature as crown-rump alone, were converted to crown-heel measurements by the use of the formula which I [12] devised in 1921. The data from these three fetuses are used in this study.

Ballantyne (1891)[13] records the vertebral levels of the larynx of two 7 months, one 8 months and two 9 months fetuses, as well as of one new-born child, and an adult in midsagittal section. The levels of the neck in the new-born than in the adult. He says, "In all probability, in the case of the new-born infant with head erect, the larynx normally extends from a point opposite to the cartilage between the body and odontoid process of the axis to the level of the upper border of the fifth cervical vertebra, or to that of the disc between it and the fourth cervical vertebra. The descent of the larynx would seem, from Symington's measurements, to be a gradual process going on throughout childhood." The trachea, according to Ballantyne, lies at a higher level in the body of the infant than in the adult. He gives its limits as extending from the body of the fifth cervical to the body of the third thoracic vertebra. Birkenbusch (1890)[14] records the vertebral levels of the larynx in the case of two new-born infants.

---

[8] Jackson: Footnote 3, second reference; Footnote 4, second reference.

[9] Merkel: Footnote 2, fifth reference.

[10] Symington: Footnote 2, seventh reference; Footnote 4, third reference.

[11] Scammon: Footnote 2, sixth reference.

[12] Noback, G. J.: Simple Methods of Correlating Crown-Rump and Crown-Heel Lengths of the Human Fetus, Anat. Rec. **23**:241, 1921.

[13] Ballantyne: Footnote 2, first reference.

Ribemont (1878)[15] illustrates a midsagittal section of a stillborn child in which the tip of the epiglottis is at the level of the lower border of the atlas and the inferior margin of the cricoid at the level of the middle of the fourth cervical vertebra.

Rudinger (1873)[16] pictures a midsagittal section of a new-born child in which the laryngeal levels are discernible.

The vertebral levels of the larynx and of the trachea in infancy and childhood have not been considered by many investigators. Symington (1887)[17] records these levels in infants 3½, 4, 6, 8 and 12 months, and in children 1 year and 10 months, 2 years and 2 months, 5 years, 6 years and in one child of 12 years. In another contribution, Symington (1881)[18] illustrates a midsagittal section of a 2 year old child in which he finds that the inferior margin of the cricoid cartilage is opposite the lower border of the fourth cervical vertebra and that the tracheal bifurcation is opposite the first thoracic vertebra. Symington concludes that the cervical part of the spinal column increases in length at a rate similar to the increases in length of the larynx, and that consequently the high position of the larynx in the neck of the child, as compared with the adult, cannot be due to its relatively small size. Symington's data are recorded in Chart 4.

Mettenheimer (1893)[19] records the levels of the inferior margin of the larynx and tracheal bifurcation in three new-born infants, and Chievitz (1899)[20] the levels of the epiglottis and larynx in two new-born children.

Birkenbusch (1890)[14] lists the vertebral levels of larynx and tracheal bifurcation in three children, 1, 6 and 13 years old, respectively.

---

14. Birkenbusch: Footnote 3, first reference.
15. Ribemont: Footnote 3, sixth reference.
16. Rudinger: Footnote 3, seventh reference.
17. Symington: Footnote 4, third reference.
18. Symington: Footnote 2, seventh reference.
19. Mettenheimer: Footnote 3, fourth reference.
20. Chievitz: Footnote 2, second reference.

Sluka (1909),[21] after pouring Wood's metal into the trachea, determined the vertebral level of the bifurcation of the trachea by means of the roentgen ray. He concluded that the level of the tracheal bifurcation, without exception, in children between 1 and 4 years, was at the fourth thoracic vertebra; i. e., at the same level as in the adult.

Piersol (1908)[22] has an illustration which shows the tracheal bifurcation in a 2-year-old child as at the level of the fifth thoracic vertebra.

Dwight (1881)[23] says, "the bifurcation of the trachea is seen opposite the lower border of the fourth dorsal vertebra. This is practically its adult position in regard to the spine." The child described was 3 years old.

Zuckerkandl (1904)[24] illustrates a midsagittal section of a 7-year-old child in which the inferior margin of the larynx is opposite the sixth cervical vertebrae and the tracheal bifurcation between the fourth and fifth thoracic vertebrae.

The most extensive work on the level of the tracheal bifurcation in infancy and childhood is that of Engel (1913)[25] who made a roentgen-ray study of 112 living children between 2 and 8 years of age. He found that, after the second year, the levels, though fluctuating, remain practically uniform.

Keibel and Mall (1910)[26] state that the larynx is much higher in the embryo and in the fetus than in the adult, and that at the time of birth the descent of the larynx is not yet completed.

Gedgowd (1900)[27] concluded that the growth of the larynx and trachea, in childhood, corresponds more to the growth of the trunk and neck than to that of the body.

The vertebral levels of the lungs of fetus and infant are barely mentioned in the literature, practically the only reference to these levels being found in an article by Jackson (1909),[28] who says, "The lungs of the 11 millimeter embryo correspond approximately to the position later of the lung apex, lying opposite the last cervical and the first two thoracic segments . . . The migration continues downward along the vertebral column, however, so that the lung in the 17 millimeter embryo lies opposite the 4th-9th thoracic vertebrae. In the 31 millimeter embryo it is opposite the 1st-10th thoracic vertebrae and in the 65 millimeter it lies opposite the 2nd-11th thoracic vertebrae." Jackson's lengths are crown-rump, and have been converted into crown-heel, for use in this study, by my method.[12]

---

[21] Sluka: Footnote 5, third reference.
[22] Piersol: Footnote 3, fifth reference.
[23] Dwight: Footnote 5, first reference.
[24] Zuckerkandl: Footnote 5, fourth reference.
[25] Engel: Footnote 4, first reference.
[26] Keibel and Mall: Footnote 2, third reference.
[27] Gedgowd: Footnote 5, second reference.
[28] Jackson. Footnote 3, second reference.

Jackson,[29] in his personal collection, has drawings of a posterior dissection of 5 day old child, made by J. A. Watkins. These show the levels of the right lung to be between the middle of the first and the middle of the tenth thoracic vertebrae, and the levels of the left lung to be between the middle of the first thoracic and the upper border of the eleventh thoracic vertebrae.

All the data mentioned in the foregoing, with the addition of two of my specimens from children, aged 5 and 8 years, respectively, are recorded in Chart 4. Included in this illustration for the purpose of comparison are the vertebral levels of the larynx and trachea of the adult as given in texts and atlases.[6]

The observations on the levels of the larynx are more numerous, owing to the number of levels that have been obtained from the illustrations of midsagittal sections. There is a range of variation in these data because different observers studied individuals whose heads were in various postures; in some cases, the head was extended; in others, it was depressed, with a consequent influence on the levels of the larynx. In my series of cases, the head was always held in the same position; i. e., so that the inferior margin of the lower jaw was at a right angle to the long axis of the body. Taken as a whole, the levels of the larynx and trachea, except for this wide variation, coincide quite closely with the results obtained by me. This may be seen on comparing Charts 3 and 4.

The material in the literature for the period of infancy is rather meager, but, as is seen in Chart 4, these data indicate that the levels of the larynx and trachea are practically the same as those in late fetal life. This continuation of similar relationship of a group of organs to the body as a whole in both fetal life and early infancy is in agreement with the conclusions of Scammon (1922),[30] who has projected the fetal weight growth curves of many organs for several months after birth, and finds that the relative increase in weight in fetal life continues through approximately the first nine months of postnatal life.

The data for childhood are also quite meager, as is indicated by their number in Figure 4. However, in spite of the small number of cases, it is evident that, during later childhood, there is a distinct descent of the levels of the larynx and also a drop in the level of the tracheal bifurcation, which begins earlier than that of the larynx.

The data for the levels of the epiglottis, inferior border of the cricoid cartilage and of the bifurcation of the trachea are also plotted in Figure 4. In the case of the adult, we find, as in earlier life, that there are few definite data. The observations recorded in the plot are from statements and illustrations in the literature. Each level observed ranges over the distance represented by three vertebrae and two disks.

---

[29] Jackson: Footnote 4, second reference.

[30] Scammon, R. E.: On the Time and Mode of Transition from the Fetal to the Postnatal Phase of Growth in Man, Anat. Rec. **22**:34, 1922.

OBSERVATIONS AND CONCLUSIONS

(*a*) *Topography of larynx, trachea and lungs during fetal life, infancy, childhood and adult life.*—The relation of the respiratory system to the vertebral column and the shifting of this system in a craniocaudal direction was studied by locating the levels of the following points: the tip of the epiglottis, the inferior margin of the cricoid cartilage, the tracheal bifurcation, the upper and lower limits of the lungs and the relation of the apex of each lung to the suprasternal notch. These levels were determined from my material on prenatal life, the new-born and two cases in children of 5 and 8 years, respectively. The literature was then examined and all available data regarding the levels of these points in the respiratory system were obtained as were also the data for infants, children and the adult.

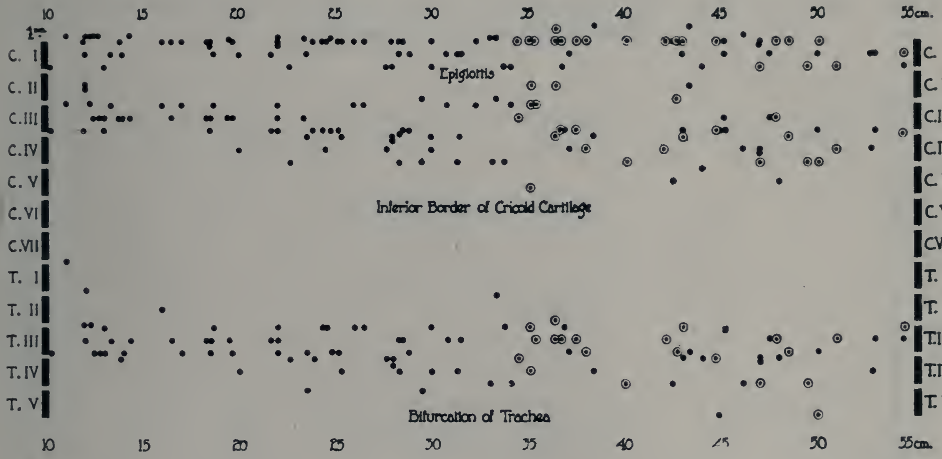


Chart 1.—Vertebral levels of the epiglottis, inferior border of the cricoid cartilage and the bifurcation of the trachea during fetal life and in the period of early infancy.

The data obtained from my material was plotted on graph paper and are reproduced in Charts 1 to 7, inclusive.

Chart 1 presents the vertebral levels of the tip of the epiglottis, inferior margin of the cricoid cartilage and the tracheal bifurcation during prenatal life and in the new-born as determined by me. The level of the epiglottis in relation to the vertebral column has a slight variation but is limited to a span of a few millimeters superior to or inferior to the first cervical vertebra. The range of the level of the tip of the epiglottis is therefore limited to a distance which may be regarded as equivalent to not more than one vertebra and intervertebral disk.

The descent of the epiglottis throughout the course of life from early prenatal to adult life is apparently as follows: The level is practically constant during prenatal life and infancy (Charts 1 and 4); a drop of two vertebrae and disks occurs between the first and thirteenth years, and a very slight descent occurs after this time, the level in the adult being quite constant.

The level of the inferior margin of the cricoid cartilage, and therefore of the inferior limit of the larynx, is less constant during fetal life and early infancy than is that of the epiglottis. In the 10 to 15 cm. group, it is located in the vicinity of the third cervical vertebrae; whereas, in the 45 to 50 cm. group, it has dropped to the vicinity of the fourth cervical vertebra. The descent is marked at all body lengths by wide variations, but as a whole it is a rather gradual one. The total drop between early fetal life and in early infancy is about equivalent to one vertebra and disk.

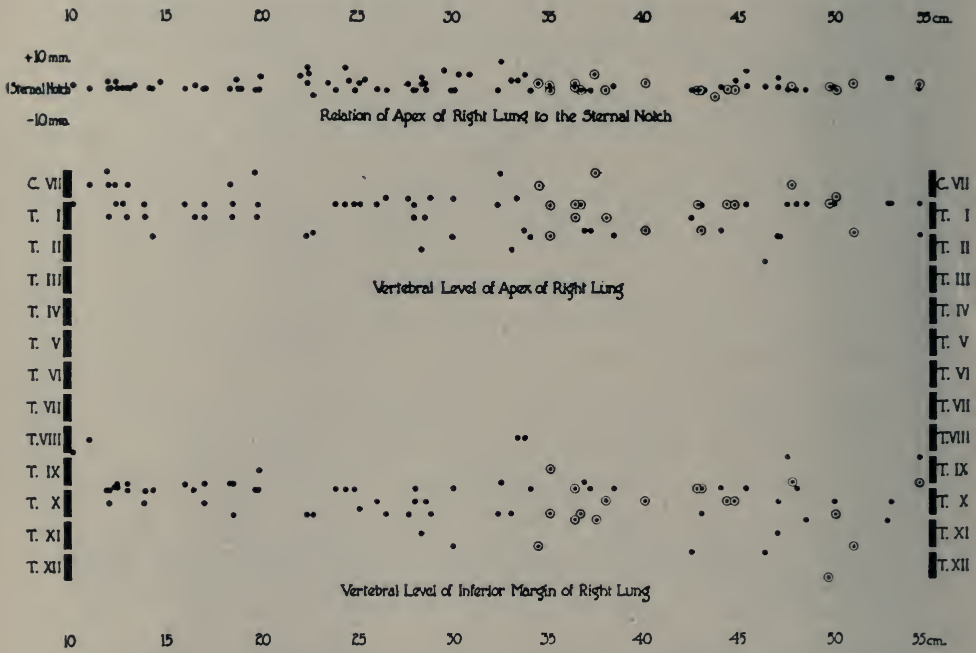


Chart 2.—The relation of the apex of the right lung to the suprasternal notch in the fetus and the new-born; the vertebral levels of the apex and of the inferior margin of the right lung.

The descent of the inferior margin of the larynx considered from early fetal through adult life begins in the fourth fetal month and continues until birth (Chart 1), a drop of about one vertebra and one disk.

This level is maintained during infancy, but another descent occurs during childhood (Chart 4), so that by the thirteenth year the inferior margin of the cricoid cartilage has descended about two vertebra and one disk, opposite to the vicinity of the sixth cervical vertebra. The adult data indicates that there is a further descent of one vertebra and disk, to the seventh thoracic vertebral level.

The level of the tracheal bifurcation in the fetus and during the period of the new-born is also less constant than the level of the epiglottis. In the 10-15 cm. group, the average level is at the third thoracic vertebra, and in the 45-50 cm. group, around the third and fourth thoracic vertebrae. There is, therefore, an appreciable descent in prenatal life of an extent of one vertebra and one intervertebral disk. The descent, as in the case of the lower margin of the larynx, is gradual from early fetal life to the end of the prenatal period.

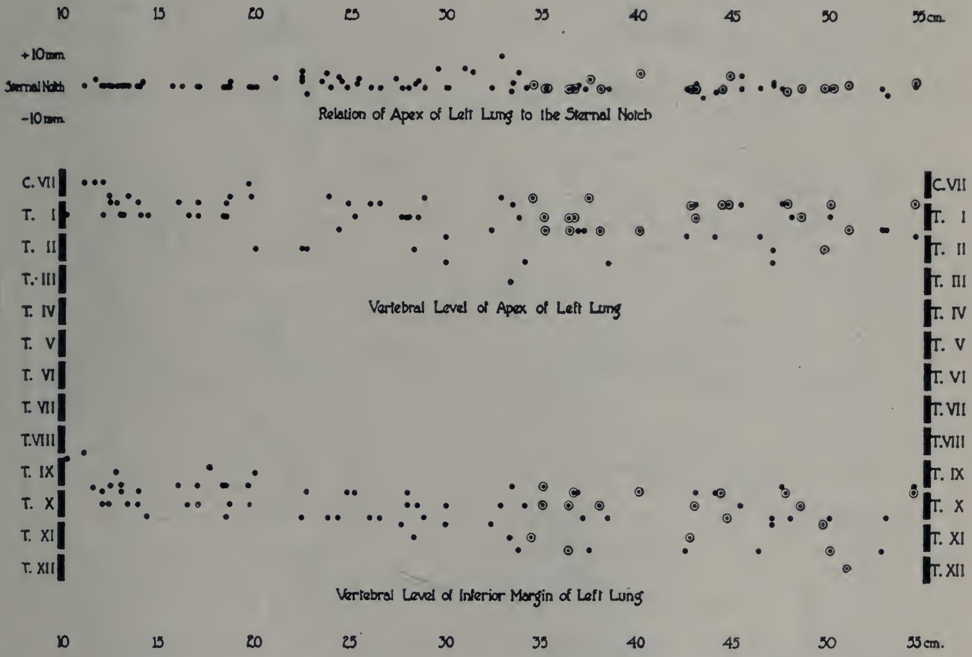


Chart 3.—The relation of the apex of the left lung to the suprasternal notch in the fetus and in the new-born; the vertebral levels of the apex and of the inferior margin of the left lung.

The bifurcation of the trachea considered from early fetal life through infancy, childhood and adult life (Charts 1 and 4) is as follows: Like the lower limit of the larynx, it begins a descent in the fourth fetal month from the level of the third thoracic vertebra to a region between the third and fourth thoracic vertebrae at birth. This level persists during the period of infancy, but early in childhood, at

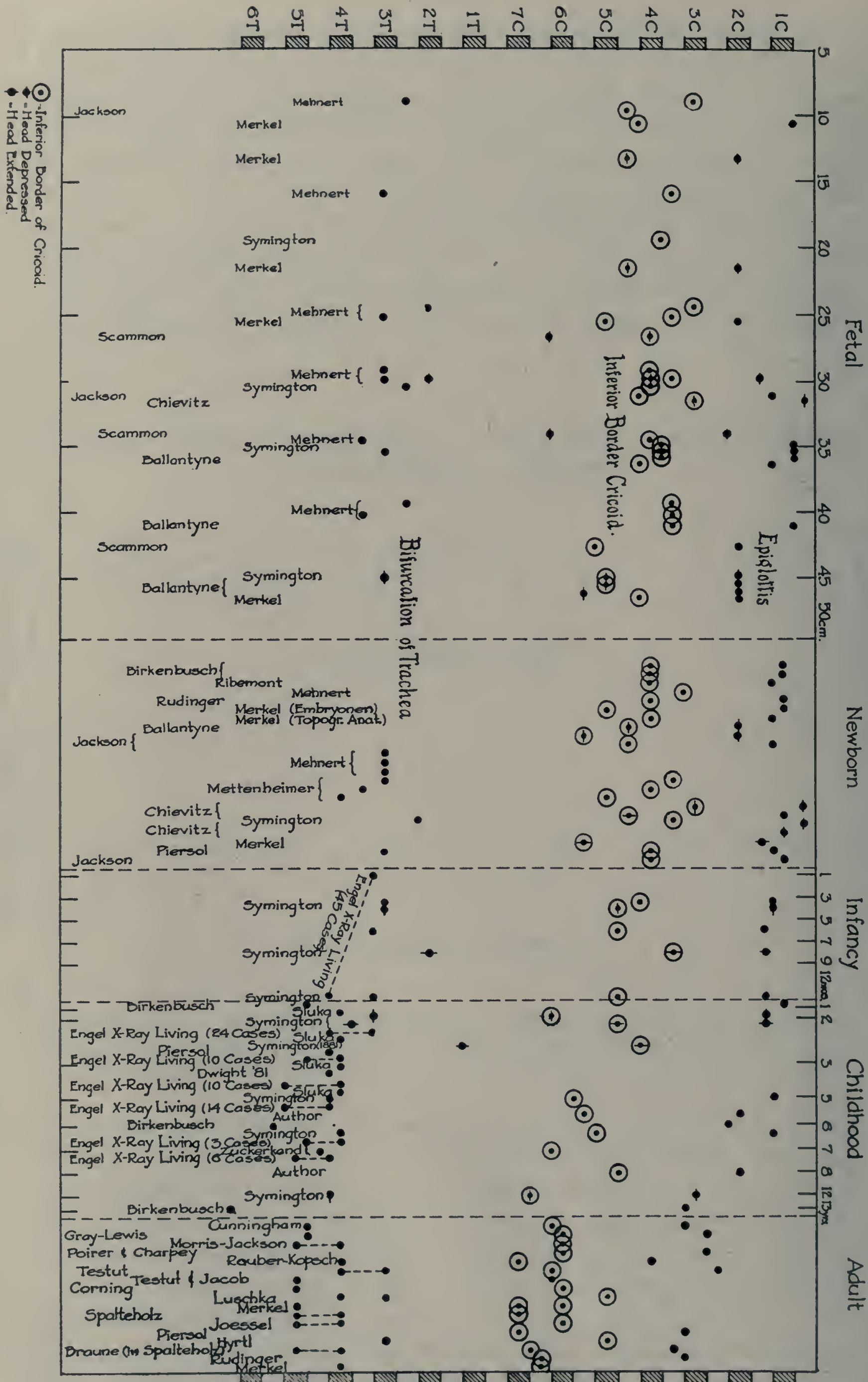


Chart 4.—The vertebral levels of the epiglottis, inferior margin of the cricoid cartilage and the tracheal bifurcation for prenatal and postnatal life as recorded in the literature.

about 2 years, another descent is apparent; and by the thirteenth year, the bifurcation has dropped a distance of one vertebra and disk to the level of the fourth and fifth thoracic vertebrae. This limit is apparently maintained during adult life.

Cameron (1922),[31] in a study of the abdominal viscera in fetal life, concludes that, of these organs, only the cecum, splenic flexure and sigmoid flexure undergo a descent in regard to the vertebral column, and Solhaug (1923)[32] finds that the bladder, uterus and ovaries of the pelvic organs descend caudalward.

In order to determine the descent of the lungs from early fetal life to the period of the new-born and in postnatal life, the uppermost and lowermost extent of these organs were noted in relation to the vertebral column and the data in the literature were surveyed. The relation of the upper poles of the lungs to the suprasternal notch was also noted. The data for the right lung are plotted in Chart 2.

The relation of the upper limit of the right lung to the sternal notch is a practically constant one during fetal life. It is found in the majority of cases to be at the same level as the notch, though there are some which extend above it, the greatest distance in these being 9 mm.

On plotting the upper limit of the right lung against the vertebral column, there seems to be a slight caudal shifting. The range is from the upper border of the seventh cervical to the inferior border of the second thoracic vertebra. The upper limit of the right lung makes a descent after the 20 cm. crown-heel length from between the seventh cervical and the first thoracic to between the first and second thoracic vertebra in the new-born, a descent of about one vertebra and disk.

The lower limit of the right lung in relation to the vertebral column shows a definite descent. In the 10-15 cm. group, the range is between the upper border of the ninth and the lower border of the tenth thoracic vertebra. From the 25 cm. length to the end of the series, the drop is distinct, as is indicated by the fact that the inferior margin of the lungs descends as low as the inferior margin of the twelfth thoracic vertebra in the full-term new-born child. The descent approximates a distance measured by one vertebra and intervertebral disk.

The relation of the left lung to the sternal notch and to the vertebral column is shown in Chart 3. The relation to the sternal notch is quite similar to that of the right lung. The majority are level with the notch though there are a number which extend several millimeters above and a few that are very slightly below it.

---

31. Cameron, A. L.: The Topography of the Abdominal Viscera in the Late Embryonic and the Fetal Period of Man as Determined by Graphic Reconstruction, abstr., Anat. Rec. **23**:12, 1922.

32. Solhaug, S. B.: A Study of the Developmental Topography of the Pelvic Organs of the Female Fetus, Thesis, Doctor of Philosophy, University of Minnesota, 1923.

The upper limit of the left lung (Chart 3) undergoes slight descent after the 20 cm. body length. Up to this length, the range is from the upper margin of the seventh cervical to the lower margin of the first thoracic vertebra. The drop from this point on to the condition as found in the new-born infant is of about one vertebra and disk, and the range extends from the upper margin of the first to the middle of the second thoracic vertebra at birth. The descent is slight, as was the case in the right lung, and it is probable that this descent is real, though it must be slight and does not occur until after the fetus has attained a length of about 20 cm. total body length, or beginning in the fifth fetal month.

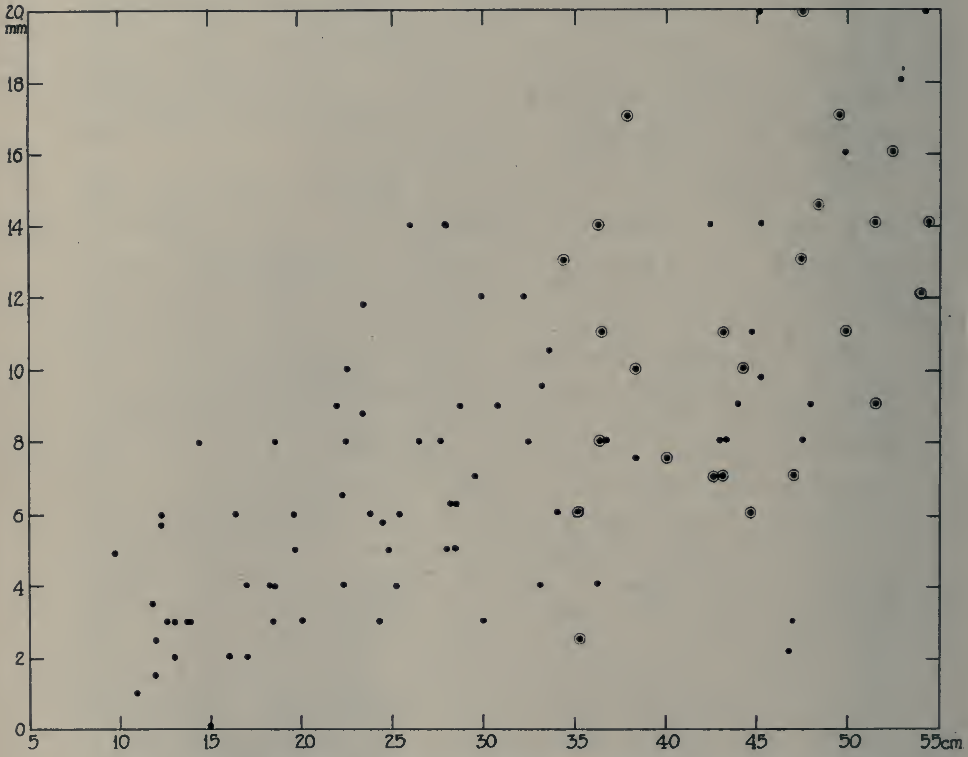


Chart 5.—Field graph of the depth of the cardiac notch plotted against total body length in the fetus and the new-born.

The inferior margin of the left lung (Chart 3), like that of the right lung, undergoes a definite descent. Up to a total body length of 20 cm., the range is from the upper margin of the ninth to the inferior margin of the tenth thoracic vertebra. From this point on, the descent is clearly indicated, and in the new-born group, the range has dropped to the levels between the middle of the tenth and the middle of the eleventh thoracic vertebra, a total drop of one vertebra and disk.

Considering both lungs, it may be concluded that the relation to the sternal notch is constant; that the upper limit of the lungs may descend slightly, and that the lower limit of the lungs, until the period of early infancy, undergoes a more definite descent of from one to two vertebrae in extent.

The vertebral levels of the adult (Chart 4) as given in the literature range as follows: The upper limit at the first thoracic vertebra and the lower limit opposite the ninth to the twelfth thoracic vertebrae. The adult vertebral levels of the lungs correspond quite closely to those found in the new-born infant. Therefore, any increase in length of the lungs in postnatal life must be accompanied by a corresponding increase in length of thorax.

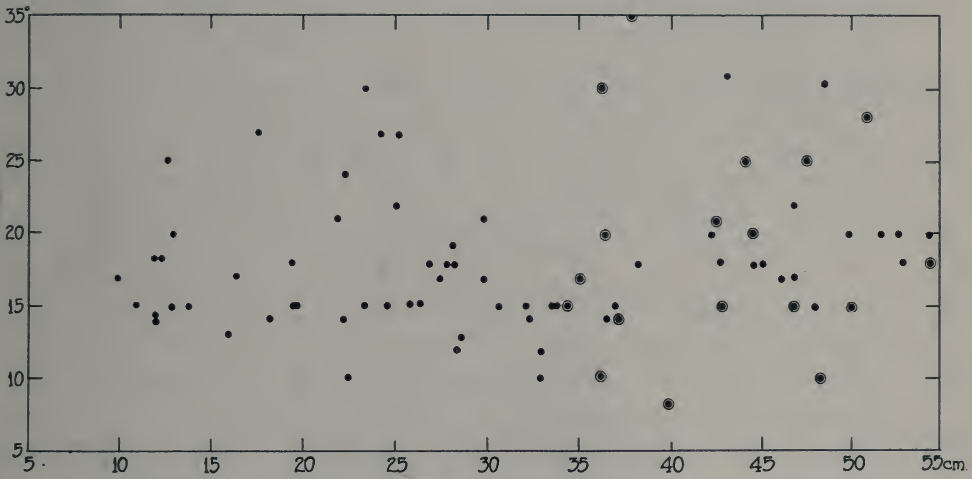


Chart 6.—Field graph of the angle of the right bronchus plotted against total body length in the fetus and the new-born.

(*b*) *The lobation of the lungs.*—Many observers have noted the variation in lobation of the lungs, notably Henle [33] who not only described them but diagrammed several of them. More recently, Spandolini,[34] in a comprehensive study of the morphology of the lungs, utilizing a series of 175 individuals, 125 adults and fifty fetuses of various stages of development, discusses lobation of the lungs.

My material consists of the lungs of a series of 101 fetuses and new-born children. It was found that the greater amount of variation

---

33. Henle, J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, 1873, Ed. 2, Vol. 2, p. 274 and Figure 207.

34. Spandolini, I.: Contributo allo studio della morphologia del pulmone, Arch. ital. di Anat. e di Embryol. **2**:604, 1913.

occurs in the right lung, since thirty-seven, or 36.8 per cent., of the total 101 right lungs were typical in their lobation; whereas, sixty-four, or 63.3 per cent., were atypical. Variation from the normal lobation in the left lung is rather infrequent, as is indicated by the fact that but 5.8 per cent., or six out of the total of 101, were abnormal in their lobation, and ninety-five, or 94.2 per cent., were typical.

The variation from the accepted normal of three lobes in the right lung and two lobes in the left lung may take form in either an increase in the number of fissures or a decrease due to their underdevelopment.

In the right lung, it was found that incomplete development of the fissures was the more frequent, with a total of sixty-one, or 60.3 per cent., of the cases showing this deficiency, and but three cases, or 2.9 per cent., presenting accessory or supernumerary fissures. The incompleteness of fissures varies greatly in extent, there being several cases of special note. One right lung had a total absence of the horizontal fissure, and the oblique fissure did not reach the base of the lung. Another modification of the fissuration of especial interest is one which was present in four of the right lungs. Here it was found that the horizontal fissure was not complete in that it failed to reach the median border of the lung, and that the oblique fissure, instead of being quite straight in its course, had, at the level of the incomplete horizontal fissure, a pyramidal tonguelike process which projected medially and inferiorly into the underdeveloped horizontal fissure. The presence of supernumerary fissures in the right lung is not frequent, there being but three cases, or 2.9 per cent., of the total number. Of these three cases there were two in which the extra fissure extended laterally from the oblique fissure at the level of the horizontal fissure to such an extent that one might say that these lungs were composed of four lobes.

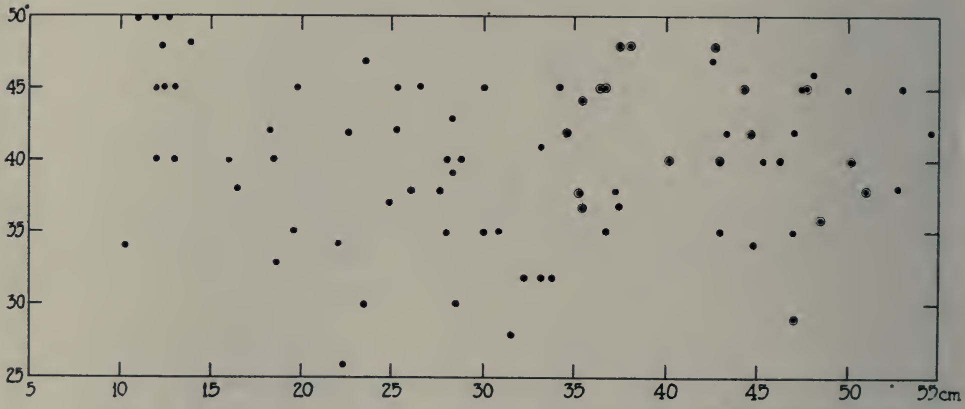


Chart 7.—Field graph of the angle of the left bronchus plotted against total body length in the fetus and the new-born.

In the left lung, abnormal fissuration is relatively infrequent, there being but six of the total of 101 left lungs with abnormal lobation. Of these, three, or 2.9 per cent., of the total had incomplete fissures, and three, or 2.9 per cent., were lungs in which there were supernumerary fissures. The latter were incomplete horizontal fissures which tended to divide the lung into three lobes similar to those normally found in the right lung.

Spandolini,[34] in his series of fifty fetuses and new-born children, found that only 49.1 per cent. of the right lungs were normal in the oblique fissure and but 36.7 per cent. of the horizontal fissures were complete. He found that the fissures in the left lung were normal in but 66 per cent. of the cases. His findings in the left lung are much higher than those in my series, in which the normally fissured lungs totaled 95, or 94.2 per cent.

(*c*) *The angles of divergence of the bronchi.*—The deviation of the right bronchus from the midsagittal plane (Chart 6) shows great variation in all of the groups of specimens. In the 10 to 15 cm. group, it ranges from 13.2 to 35.8 degrees, and in the new-born group, from 10 to 30 degrees. However, throughout fetal life, the greater number of cases are grouped between 14 and 22 degrees and the average may be taken as about 18 degrees.

The deviation of the left bronchus from the midsagittal plane, like that of the right bronchus, varies to a great extent, and the angle is much greater than is that of the right bronchus. The range (Chart 7) in the 10 to 15 cm. group is from 34 to 50 degrees and in the new-born infants from 38 to 45 degrees. The average angle for the left bronchus may be stated to be about 42 degrees.

(*d*) *The cardiac notch.*—The cardiac notch (Chart 5) shows a tendency to increase in size along with the increase in total body length, there being, however, very wide fluctuations in this measurement throughout the fetal period. The measurement in the 10 to 15 cm. group is from 1.0 to 6.0 mm., and, in the new-born group, ranges from 2.0 to 20.0 mm.

SUMMARY

1. The descent of the respiratory system in relation to the vertebral column during childhood is not peculiar to this period in the development of the individual. It is merely a stage in a process which is already manifested in early fetal life and which continues to operate through infancy, childhood and maturity.

2. The larynx. During fetal life, the topography of the epiglottis shows practically no change. It remains quite constantly opposite the first cervical vertebra. This level persists through infancy and child-

hood until puberty, when the adult relationship is attained, i. e., it lies opposite the third cervical vertebra.

The inferior margin of the cricoid cartilage, and therefore the lower limit of the larynx, descends during the course of prenatal life from opposite the third to opposite the fourth cervical vertebra, a distance represented by one vertebra and intervertebral disk. During infancy, this relationship remains constant; but during later childhood, another descent to the level of the sixth cervical vertebra takes place, a drop of two vertebrae and one disk. With the attainment of maturity, a further descent of one vertebrae and disk has occurred, so that the inferior limit of the larynx is then opposite the seventh cervical vertebra.

3. The bifurcation of the trachea. The tracheal bifurcation undergoes a descent caudalward in relation to the vertebral column during fetal life. It drops from opposite the third to opposite the fourth thoracic vertebra, a descent of one vertebra and disk. The natal relationship persists during infancy, but in childhood another descent takes place, and by puberty the bifurcation is opposite an area between the fourth and fifth thoracic vertebrae. This level is then maintained, apparently, through adult life.

4. Topography of the lungs. The apices of the lungs remain at practically the same level as the suprasternal notch throughout the course of fetal life.

The upper poles of the lungs in relation to the vertebral column undergo a slight descent during prenatal life from a level opposite the seventh cervical or first thoracic vertebra to the upper margin of the second thoracic vertebra, a distance of one vertebra or less. This level is apparently maintained throughout the course of postnatal life.

The inferior margins of the lungs during fetal life undergo a descent from between the ninth and tenth to opposite the tenth to twelfth thoracic vertebrae, a distance equivalent to slightly more than one vertebra and disk. The latter level, present at birth, coincides quite closely to the levels as given in the standard texts and atlases for the adult, thus indicating the probability that the postnatal growth in length of the lungs is closely correlated with the increase in length of the thorax.

5. The lobes of the left lung in the human fetus do not vary much from the condition in the adult, there being but 5.8 per cent. of the total with atypical lobation. The lobes of the right lung depart quite markedly from the conditions usually described in the adult, there being but 36.8 per cent. of the total with the typical three-lobed condition.

6. The depth of the cardiac notch. The extent of the cardiac notch during prenatal life is extremely variable in a group of cases of the same body length. There is, however, a general increase in depth with increase in total body length.

I wish to express my sincere thanks to Dr. R. E. Scammon for his kind advice and assistance in this study, and to Dr. C. M. Jackson for many valuable suggestions.

Reprinted from the American Journal of Diseases of Children
December, 1923, Vol. 26, pp. 515-533

Copyright, 1923
American Medical Association
Five Hundred and Thirty-Five North Dearborn Street
CHICAGO

diffuse fibro-epithelial tumor associated with fibro-adenoma are features described in the literature. Malignancy is rare, but is recorded.

Pathologically, most cases fall into two groups: (1) fibro-epithelial (often associated with fibro-adenomas) and (2) adipose. Two cases of each type from the Mayo Clinic series are reported in detail. The patients with fibro-epithelial hypertrophy were a girl of fifteen years and a woman of thirty-six whose hypertrophy began with pregnancy. The adipose hypertrophies occurred in a virgin of nineteen years and a parous woman of forty-one years whose hypertrophy was not associated with pregnancy. The adipose type is rare; only four cases have been previously recorded.

The fibro-epithelial hypertrophies were associated with fibro-adenomas, succulence of the preponderant fatty tissue, rapid proliferative changes in the fibro-adenomas, and reproductive activity in the mammary acini (primary cytoplasia of MacCarty). The acinar groups were invaded and broken up by growing fibrous tissue.

The adipose type was characterized by the relative absence of acini and a preponderance of fat. A few fibrous bands traversing the fat carried a moderate number of acini showing primary cytoplasia. The epithelium in both types was hypertrophied to a variable degree.

The etiologic factors are not clearly understood, but the evidence suggests an endocrine dyscrasia probably of the ovarian type.

To be differentiated in diagnosis are intracanalicular myxoma and fibroma, sarcoma, elephantiasis, and the fatty breasts of obesity.

If spontaneous regression fails to occur after a reasonable length of time, surgical amputation may be indicated.

POSTNATAL CHANGES IN WEIGHT AND STRUCTURE OF THE REPRODUCTIVE TRACT IN THE FEMALE ALBINO RAT*

HJALMAR L. OSTERUD

This study deals with the changes in weight and in general structure of the ovaries, uterine tubes, uterus, and vagina of the albino rat during the period of postnatal growth, primarily from birth to sexual maturity.

The normal growth and variability of the body and of the various systems and organs in the albino rat have been carefully investigated by Donaldson, by Jackson and Lowrey, by Jackson, and by Hatai. In Jackson's and Hatai's work the ovary has been included, but so far as the writer is aware, no study of this kind has been made of the growth of the tract as a whole, including the uterine tubes, uterus, and vagina.

Numerous published researches deal in other ways with the reproductive organs of the rat such as those of Coe, Kirkham, Kirkham and Burr, and Sobotta and Burckhard on the maturation, ovulation, and fertilization of the ovum; Lane-Claypon on oögenesis and the interstitial cells; Belloy on the corpus luteum; Hatai on results of gonadectomy; Frank and Corner and Warren on the corpora lutea, and the formation of deciduomas; Arai on the number of ova; and the extensive series of studies by Long and Evans on the oestrous cycle and allied problems. The complexity of growth during the postpuberal period makes necessary the employment of different methods for its analysis; consequently this later period is dealt with only incidentally.

MATERIAL AND METHODS

A series of 180 female albino rats were used, of which 155 have furnished data with regard to organ weights. In age the rats range from newborn to three hundred days; in body weight, from 2.7 to 294 gm. Thirty had given birth to one litter each, at periods varying from twelve hours to three months before being sacrificed. The remaining 125 animals were virgins, kept isolated from males. The serially sectioned ovaries of thirty-two rats (ranging from 4.6 to 255 gm. body weight) were subjected to a volumetric determination of their various structural components, in an attempt to ascertain the relative part played by each component in the growth of the organ. Jackson's paper method was employed. This consisted of projecting every fifth, eighth, tenth, or twelfth section of the organ, as the case might require, on special paper of uniform weight, outlining the elements desired under uniform magnification for any one series, then cutting out, segregating, and weighing the total amounts of paper representing each of the elements. Thus the percentage volumes of the surface layer, follicular tissue, follicular cavities, interstitial tissue, corpora lutea, and connective tissue stroma can be quite accurately determined.

---

* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1922. From the Department of Anatomy, University of Minnesota, Minneapolis.

Zenker's, Fleming's and Bouin's fluids, and formalin were used as fixatives. The entire ovaries and tubes were sectioned serially in paraffn. Of the uterine horns and vagina only a representative middle region was sectioned. Iron-hematoxylin, Delafield's hematoxylin, and eosin were used as stains.

WEIGHT CHANGES IN THE GROWTH OF THE REPRODUCTIVE TRACT

Growth in weight of the ovaries.—The postnatal growth in weight of the ovaries has been described by Jackson and by Hatai. The data are compiled by Donaldson. With their results the present study is in general agreement. It has been repeated chiefly for purposes of correlation with the rest of the reproductive tract.

By plotting the absolute weights of the ovaries on coördinate paper, it is seen that there are three points in the life of the rat when the growth of the ovaries makes a decided change in rate. These occur approximately at 30, 55, and 140 gm. of body weight. After a brief initial period of relative retardation, the first growth period (from birth to 30 gm. body weight and twenty-five to thirty days of age) exhibits an increase in the weight of the ovaries at a rate greater than that of the body as whole. At birth the percentage weight (ovarian weight divided by body weight) averages about 0.017 per cent of body weight (Fig. 102), agreeing well with Jackson's data. However, variability is great. During the first two weeks the relative weight generally falls below that at birth, individual cases reaching a low level of 0.0057 per cent of the body weight. During the third and fourth weeks the relative weight rises rapidly reaching a value of about 0.030 per cent in rats weighing 28 to 30 gm. and twenty-five to thirty days old.

Arai has shown that the greatest decrease in the number of ova in the rat's ovary occurs in the first twenty-three days of life, after which the rate of decrease becomes markedly less. There is definite correlation between this disappearance of ova and the growth of the ovary, which will be considered in connection with the structural changes occurring at this time. Roughly speaking, by the end of this initial growth period the ovaries have grown twice as much as the body.

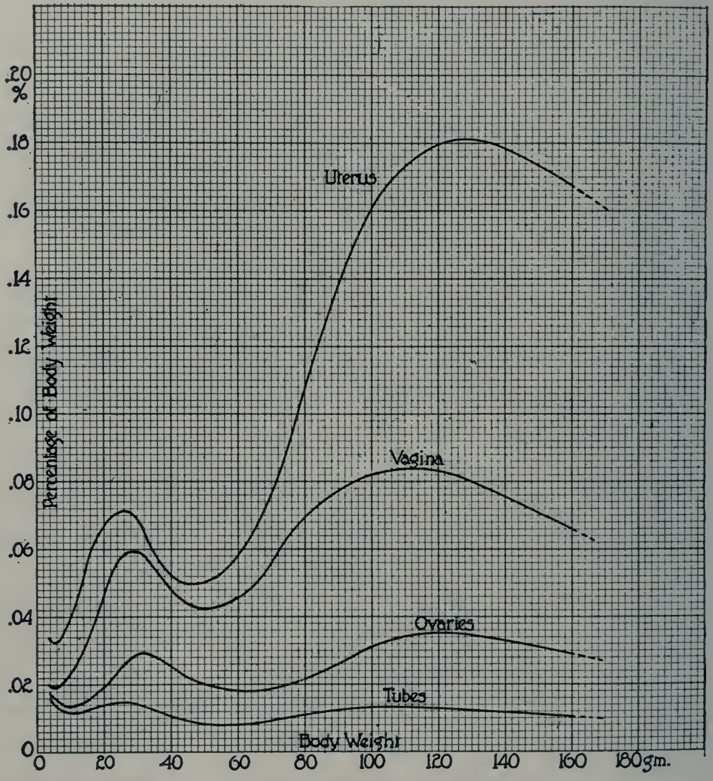


Fig. 102.—Postnatal changes in weight and structure of the reproductive tract in the female albino rat.

From about 30 to 55 gm. body weight, there follows a second period during which the rate of ovarian growth is much diminished. Jackson described this actual decrease in relative weight of the ovaries, his data indicating a drop from 0.030 to 0.015 per cent. The value obtained in the present data is 0.017 per cent. The body as a whole outgrows the ovaries, so that at 55 gm. body weight, the ovaries are of a relative size about equal to that at birth (Fig. 102).

At about 55 gm. body weight a third growth period sets in, another period of acceleration, marking the prepuberal and puberal growth and extending through the establishment of sexual maturity, or until a body weight of 130 to 140 gm. is attained.

Sexual maturity, as expressed by ovulation, appears to fall usually about the middle of this period, in rats of 90 to 100 gm. in body weight. The variation in the ovarian weights now increases markedly so that a field graph of the absolute weights presents a conspicuous scatter. At the end of the period the relative weight of the ovary has reached an approximate mean value of 0.035 per cent.

Beyond this point of 140 gm. body weight, the absolute weight of the ovaries continues to increase variably but the relative weights indicate that the fourth period is again one of retarded growth. The variability in ovarian weights becomes still more marked, attributable to the great variability induced by the structural and functional changes of the ovaries throughout the sexual cycles.

Growth in weight of the uterine tubes.—At birth the ovary is partially enclosed in a peritoneal fold, which, as growth proceeds, gradually covers the ovary, forming finally a thin peri-ovarian capsule, which isolates the ovary from the body cavity. In this capsular fold the uterine tube develops. The complex coiled form of the adult tube is not found at birth; instead the tube has the simple form of an undulating letter C. The early growth of the tube in length is very marked and out of proportion to the distance between its extremities. Consequently a greatly convoluted tube is eventually developed, reaching approximately its complete form in about ten days. By the time sexual maturity is reached, the tube, instead of partially encircling the ovary, has become a compact, coiled mass, much smaller than the ovary, and lying at the side of the hilus. Sobotta found in the mouse, and Long and Evans in the rat, that the peri-ovarian capsule becomes distended with fluid during œstrus.

Growth in weight of the uterus.—It has been found that the postpartum involution of the uterus in the rat is approximately completed at the end of a week following delivery; consequently no data from primiparous rats, prior to the eighth day, are considered in the weight changes of the uterus.

When graphically represented, the weights of the uteri of the rats reveal again a general correspondence in growth with that of the ovaries. The numerical values indicate (by comparison) that the amount of retardation in the second period is less, but that the acceleration during the third period is much greater than in the tubes and ovaries. Comparison of the percentage weight of the uterus at birth with that of the other points in the life cycle seems to indicate that the uterus is relatively underdeveloped at birth as compared with the ovaries.

When the prepuberal growth sets in, the variability increases rapidly, on account of the great fluctuations in weight of the uterus during the sexual cycles. Present data indicate that greatest variability occurs in rats from 160 to 200 gm. body weight. The lowest extremes in normal uterine weight are associated with postpartum involution. Distinct undernutrition also markedly affects the uterine weight.

Growth in weight of the vagina.—In the growth of the vagina the changes in weight follow the behavior of the other generative organs, with corresponding phases. The vagina of the newborn rat is closed and its opening is associated with the first ovulation. A rat at 77.3 gm. body weight was the smallest to display the open vagina. In rats approaching their first ovulation the uterus distends with fluid, a condition which Long and Evans have noted as characteristic of the preœstrous and œstrous phases of the cycle. It seems possible that this fluid may play a part in the opening of the vagina.

Haldeman has carefully described the histologic processes involved in this opening, but does not mention the condition of uterine distention. In intensity of postnatal growth the vagina ranks next to the uterus, exceeding the ovaries and tubes.

Discussion of weight changes.—As appears from the foregoing account, except for minor or doubtful variations, the various parts of the reproductive tract follow a similar type of postnatal growth. After a brief initial period of retardation, growth, up to a body weight of 28 to 30 gm., is very rapid; from 30 to 55 or 60 gm. it is distinctly retarded; from 60 to 130 or 140 gm. again accelerated, with the first ovulation occurring as early as the middle of the period; and finally, after 140 gm. there is a general retardation. Growth in the various parts of the tract is by no means proportionate. It is therefore conceivable that factors, experimental or otherwise, capable of affecting the growth of the generative organs, may have different and varying degrees of influence, depending on the phase of growth of the organs.

In the postnatal growth of the human uterus there occurs during the first two years a very marked involution with which there appears to be nothing comparable in the rat. The relative loss in weight of the rat's uterus is not due to an absolute loss as in the organ of human beings, but merely to a growth slower than that in the body as a whole. Moreover the duration of the low weight level of the uterus in the rat is too short to offer satisfactory correspondence.

STRUCTURAL CHANGES IN THE GROWTH OF THE REPRODUCTIVE TRACT

Structural changes in the ovary.—During the postnatal growth, the ovary undergoes a series of definite histogenetic changes which bear definite relationship to the changes in weight of the organ. The ovary in the new-born exhibits a single-layered germinal epithelium, which is still actively supplying primary ova to a distinct subgerminal zone, inside of which a tunica albuginea is in an early stage of differentiation. The large bulk of the ovary consists of irregular cords and masses of epithelial cells, more or less radially arranged. Primitive ova and indifferent cells are readily made out, the former very prominent because of the nature and arrangement of the chromatin (pachytene diplotene, and dictyate stages of von Winiwarter and Sainmont). Differentiation of the ova and their primitive follicles proceeds from the periphery inward. This early proliferation of primitive oöcytes is interpreted as the end of the fetal proliferation, which soon ceases, and is replaced by a new proliferation of "definitive" oöcytes from which the peculiarly prominent nuclear changes are conspicuously absent. The primitive ova are all destined to disappear by degeneration. The degeneration of ova is already under way at birth, regressive nuclear changes being readily seen in the interior of the ovary. By three days of age the primitive ova have nearly all lost the peculiar nuclear characteristics and by the end of the first week the cell cords become broken up and the primitive ova completely isolated, each with its own follicle. Mitotic figures in the cells of all the ovarian tissues give evidence of increasing growth.

By the end of the first week the proliferation of definitive oöcytes is well under way and a fairly distinct boundary may be made out between the younger definitive oöcytes at the periphery and the older and further developed primitive oöcytes of the interior. This boundary is soon obliterated through the active growth of definitive oöcytes and degeneration or arrested differentiation of the primitive oöcytes. Expansion of the central mass of primitive oöcytes and their follicles becomes more and more conspicuous, and with the increasing atresia of the follicles occurs a rapid proliferation of the interstitial tissue. Arai has shown that the loss of ova in the rat during the first ten days is approximately 20,000 (from 35,000 to 15,000), or nearly two-thirds of the total number.

In spite of this decrease in number of ova, the ovary continues to grow in size and soon does so at a rate considerably greater than that of the body as a whole. Conspicuous in this growth is the development of the follicular apparatus and the increasing production of interstitial tissue.

While follicular growth is plainly increasing, so is also follicular atresia. By the time the rats have reached a body weight of 16 to 19 gm., the larger part of the primitive oöcyte generation has undergone degeneration and a considerable part of the follicular apparatus belongs to the postnatal definitive generation.

By the end of the third week practically every one of the larger follicles gives evidence of atresia. The follicles have become much larger and their walls thinner, chiefly due to the increase in liquor folliculi. From some follicles the ova have entirely disappeared, in others they may be seen floating freely in the fluid of the antrum. Large compact masses of interstitial tissue gradually replace the disappearing follicles. During the third week a spurt of follicular growth again takes place, only to be followed by increasing atresia. Some of the ova undergo a peculiar fragmentation simulating segmentation, even with nuclear inclusions in the several fragments, a condition similar to that described by Kingery in the mouse as an abortive first maturation division.

By the end of the first growth period the amount of follicular degeneration comes to a climax, never again exhibiting these phenomena in such extreme degrees. This corresponds with Arai's findings in his counts of ova, the first great reduction of ova coming to an end at this time. At the periphery of the ovary, however, new definitive oöcytes are still being produced by the germinal epithelium, although perhaps at a reduced rate.

During the first growth period, therefore, the major part of ovarian differentiation has been accomplished, all prepuberal elements have been established, and ova have come near enough to maturity to reveal abortive attempts at maturation, while the ovary has been growing at a rate never to be duplicated and while the ova have been undergoing their greatest reduction in number.

OVARIAN CHANGES IN THE SECOND GROWTH PERIOD

At the beginning of the second growth period the rate of growth is greatly decreased, a decrease correlated with a similar reduction in the rate of degeneration of ova. Arai estimated an insignificant decrease from 10,746 to 10,185 in the number of ova. This period is further characterized by a recovery from the extreme degree of atresia which previously appeared, and by an increased amount of follicular development. Reciprocally there is a decrease in the rate of development of interstitial tissue. The follicles about the middle of this period are conspicuously thick walled, thicker walled for their size than at any other time. In consequence the follicular tissue (stratum granulosum) attains its greatest relative volume during this period. The recovery of follicular growth is, however, only transitory, for atresia sooner or later overtakes even the most robust follicles and by the end of the period degeneration of follicles is again plainly increasing, and again accompanied by an increase in interstitial tissue. The largest follicles, however, attain a size only slightly smaller than that of the fully mature follicle as seen later.

Alternately processes of development and of degeneration apparently hold forth, and progressive and regressive processes are revealed in both follicular and interstitial tissue. One thus observes a complex rhythm of morphologic changes in the ovary which on the one hand bring the ova and their follicles successively nearer maturity, but still fall somewhat short of this goal, and on the other hand maintain a balance, which, seemingly, is both internal, between the ovarian constituents themselves, and external, between the ovaries and the rest of the body. Barring individual variation, the upper and lower ovarian weight extremes appear to bear definite relations to the maximal and minimal phases of structural differentiation.

OVARIAN CHANGES IN THE THIRD GROWTH PERIOD

During the earlier part of this period the structural changes in the ovary are mainly quantitative. Some of the largest follicles exhibit a decidedly robust appearance, with less evident signs of atresia than previously met with. For their size they are not so thick walled as those of younger ovaries. On the whole they give greater promise of attaining maturity than any follicles of preceding growth phases. But atresia is clearly increasing in other follicles and even some of the promising follicles eventually succumb to the degenerative processes. Volumetric determinations show that reduction of follicular tissue is actively under way and that the interstitial tissue is entirely reponsible for the increasing rate of growth of the first half of the period. Arai has shown that at this time there is an increased reduction in number of ova.

The animals, however, attain sexual maturity, some earlier, others later in the period, so that finally some of the follicles and ova come to full maturity and ovulation takes place with formation of corpora lutea. The development of the corpora lutea continues the rate increase begun by the augmented growth of interstitial tissue. Apparently the capacity of the germinal epithelium to produce new definitive oöcytes has by this time been largely exhausted. In one of the rats in which some ova were in the stages of genuine maturation division, distention of the uterus with fluid also occurred and the vagina was still closed.

The first ovulation may not always be perfectly successful as evidenced by failure of the ovum to be extruded, later to be found within the developing corpus luteum. By the end of the third period several ovulations may have occurred and several generations of corpora lutea may be present. The advent of the œstrous cycle introduces complexities into the structure of the ovary, which furnish ample evidence as to the cause of the great variability in weight of the organ. At about 130 to 140 gm. body weight the rate of growth of the ovary rapidly diminishes, apparently in association with a condition of balance within the organ between its progressive and regressive processes.

OVARIAN CHANGES IN THE FOURTH GROWTH PERIOD

The present data indicate that the ovaries continue to grow although at a constantly decreasing rate throughout the fourth period. The largest ovaries were found in a rat of 193 gm. The proportions of the constituent elements vary with the phases of the sexual cycle. The interstitial tissue, which reached its maximal relative development just before the first ovulation, is gradually reduced in amount through active differentiation of the tissue. Follicular degeneration even among large follicles still goes on. There is much in the behavior of the regressive processes, especially in ovaries of virgin animals which have ovulated repeatedly for some time as compared with the ovaries of primiparous animals, which raises the question as to the normality of so much degeneration. Heape in his work on the rabbit thought that increased atresia, which might apparently lead to sterility, was noticeable in the does that were kept away from the males over several œstrous cycles.

CHANGES IN THE VOLUMETRIC RELATIONS OF THE OVARIAN CONSTITUENTS

The surface layer of the ovary (including germinal epithelium, subgerminal zone of oöcytes, and tunica albuginea) totals about 8 per cent of the ovarian volume at birth. By the end of the first growth period this has been reduced to about 2 per cent, which value falls gradually through the other periods. This decrease is primarily due to the loss of young ova and indifferent cells in the exhaustion of the germinal epithelium.

At birth the ova total about 57 per cent of the ovarian volume. This is reduced to about 2 per cent during the first growth period, followed by slow reduction through the other periods.

Follicular tissue increases rapidly to a value of about 34 per cent in rats ten days old, after which the increasing follicular atresia brings about a decided reduction in relative volume to about 22 per cent toward the end of the first period. During the second period follicular volume increases to a maximum of 38 per cent. From this value there is a gradual general reduction throughout the third and fourth periods.

The follicular cavities assume prominent volumetric relations at two points in the growth of the ovary, having increased to about 11 per cent by the end of the first growth period, being then sharply reduced to about 6 per cent, and increasing to about 20 per cent just before the first ovulation, after which there is apparently a slow general reduction, but great variability due to œstrous phases.

The volume of interstitial tissue increases rapidly to about 57 per cent during the first growth period, being the only element of the ovary completely correlated with the great ovarian growth of this period. During the second period the interstitial tissue suffers a relative loss in volume, reciprocal with increase in follicular tissue. In the third period it increases rapidly to a maximum of about 43 per cent just before the first ovulation. The relative volume is suddenly reduced at this point by the development of corpora lutea, but in general there is a slow gradual decrease in volume throughout the rest of life.

The connective tissue stroma plays a more passive volumetric part and increases more gradually from about 7 per cent at birth to 30 per cent at the end of the series.

The sudden development of the corpora lutea naturally affects the relative volume of all other constituents. By the end of the third period a value of about 42 per cent has been reached, which is apparently fairly constantly maintained, with fluctuations above and below this value incident to the influence of the sexual cycle.

Structural changes in the uterine tubes.—While the changes in weight of the uterine tubes, uterus, and vagina show that these organs follow the ovarian type of growth (Fig. 102), none of these undergoes so marked a structural differentiation as is characteristic of the various growth phases in the case of the ovary. Except for changes incident to the œstrous cycle, the growth of the tubes, uterus, and vagina is more quantitative than qualitative.

At birth the uterine tube is very simply coiled. It is then relatively thick walled with a very small lumen lined by a simple columnar epithelium, not unlike that of the adult tube except for absence of cilia, and is similar in structure throughout its length. In the wall the differentiation of lamina propria and muscularis is just barely discernible.

Growth in length is most conspicuous, producing the extensive coiling of the tube in about ten days. In diameter the lower half of the tube increases four or five times from birth to adult, the muscular wall becoming relatively thin, and the upper half only two or three times, its muscular wall becoming relatively thick. When sexual maturity approaches, the usually thin lamina propria hypertrophies and becomes edematous, the epithelial cells of the lining becoming twice their former height in their assumption of secretory activity.

Differentiation of the tubes is, therefore, a gradual process, in which the quantitative changes probably occur in response to the influence of the ovary.

Structural changes in the uterus.—As in the tubes, the structure of the uterus of the newborn rat is very simple. The lumen is, however, relatively much larger. The endometrial epithelium is simple columnar, similar to that of the resting adult uterus. Differentiation into endometrial lamina propria and muscularis is just beginning. In a week's time the main layers of the uterine wall have been definitely established and the formerly more rounded lumen is given a more elongated vertical slit-like form. Diverticula of the lining epithelium begin to grow down as the first fundaments of the glands at about ten days of age. The musculature comes to occupy about half the thickness of the uterine wall, with a thick inner circular and a thin outer longitudinal layer. More slender, tubular glands grow out from the parent diverticula and become slightly coiled, so that by the end of the first growth period when uterine structure is well established, eight or ten glands may be counted in a transverse section.

Until the accelerated growth of the third period sets in there is not much change in the uterus except for a slight increase in the number of glands. When prepuberal growth begins and œstrus approaches, the mucosa undergoes a marked thickening, with distinct hyperplasia and with some hypertrophy, later augmented by congestion. The epithelium of the mucosa and of the glands becomes markedly taller, the cells revealing by their staining reaction the approach of secretory activity. As secretion progresses, the uterus distends with fluid, the epithelial cells increase in width with the stretching of the lining, and the lamina propria and the muscularis become reduced in thickness.

When secretion ceases and the fluid is evacuated, degenerative changes appear in the epithelial cells, followed by desquamation and by immigration of leukocytes. The lumen becomes filled with cell débris and secretion. These changes during the œstrous cycle have been described by Stockard and Papanicolaou in the guinea pig, by Long and Evans in the rat and by Allen in the mouse.

During the fourth period the uterus presents successive series of these structural changes. The uteri of virgin females do not appear to return to a size or structure wholly comparable with that before œstrus, and successive œstrous cycles seem to result in a characteristic summation in weight and structure of the uterus, the uteri sometimes reaching immense size. Compared with uteri of younger animals or with post-partum uteri after involution in animals of about the same age and weight, there are several striking differences. The mucosa is unusually thick (up to four times that of the muscularis) and greatly hyperplastic; the number of glands is markedly increased; the muscularis is only half its normal thickness. The ovaries are filled with old, small, involuting corpora lutea and huge degenerating follicles. The questions arise: are these phenomena common to all female rats during their sexual life or are they the expressions of a response to something abnormal? Is it possible that continued succession of active œstrous cycles induces in the organs of these virgin animals a structural condition inconsistent with proper reproductive function? Heape suggested that withholding the male rabbit from the female during several successive heat periods induces degeneration of the follicular apparatus, making the female liable to sterility. There is much in the structure of both ovaries and uterus in postpartum females to suggest that pregnancy with its subsequent involution restores these organs to a certain balance in structure more like that of younger animals.

Structural changes in the vagina.—At birth the vagina is similarly poorly differentiated. The differentiation of muscularis and lamina propria follow approximately that of the uterus. At birth the vaginal epithelium is two layered, low columnar. By the end of the first growth period it has become three or four layered, and by the end of the second period four or five layered. During the third period the epithelium thickens rapidly to seven or eight layers of cells, assuming a stratified squamous structure. With approach of œstrus the surface layer becomes tall, columnar, and of secretory function. Leukocytes accumulate in the stroma and begin to migrate through the epithelium. The tall superficial cells finally degenerate and desquamate and a large number of leukocytes enter the lumen of the vagina. After this desquamation a typical stratified squamous epithelium remains. The vagina therefore undergoes just as striking œstrous changes as does the uterus. These changes have been described by Morau in the mouse and other rodents, by Stockard and Papanicolaou in the guinea pig, by Long and Evans in the rat, and recently by Allen in the mouse.

DISCUSSION OF THE STRUCTURAL CHANGES

It is clear that it is the ovary in which structural and weight changes are most closely correlated. The ovary probably dominates the growth of the other organs in the way of making the quantitative changes in these follow the quantitative changes in the ovary. In the absence of the ovary (as shown by extirpation experiments) such quantitative changes do not occur.

Proliferation of oöcytes from the germinal epithelium continues approximately up to sexual maturity in the rat, but no separate prepuberal proliferation has been observed.

The great amount of follicular atresia and the large part played by the interstitial tissue in the quantitative growth changes is especially striking in the rat and must be of fundamental significance. From a structural standpoint the interstitial tissue offers no positive evidence as to endocrine function, although the quantitative relations show a parallelism in the growth of this tissue and that of the generative organs, especially in the periods of acceleration. Whatever the forces be that promote or check the growth of the generative organs, to consider these processes apart from the body as a whole, or apart from organs which are known to exert positive influence on the reproductive tract, would therefore appear irrational.

BIBLIOGRAPHY

1. Allen, E.: The œstrous cycle in the mouse. Ovogenesis in the sexually mature mouse. Anat. Rec., 1921, xxi, 43–44.

2. Allen, E.: The œstrous cycle in the mouse. Am. Jour. Anat., 1922, xxx, 297–371.

3. Belloy, G.: Recherches sur l'origine des corps jaunes de l'ovaire chez le rat et le cochon d'Inde. Compt. rend. d. l'Ass. d. Anat. Première session, 1899, Paris, 47–52.

4. Coe, W. R.: The maturation of the egg of the rat. Science, 1907–1908, n. s., xxvii, 444.

5. Donaldson, H. H.: The rat; reference tables and data for the albino rat (mus norvegicus albinus) and the Norway rat (mus norvegicus). Philadelphia, 1915 (Wistar Inst.), 283 pp.

6. Evans, H. M.: On the behavior of the ovary and especially of the atretic follicle mammalian towards vital stains of the acid azo group. Anat. Rec., 1916, x, 264.

7. Evans, H. M., and Bishop, Katherine S.: On an invariable and characteristic disturbance of reproductive function in animals reared on a diet poor in fat soluble vitamine A. Anat. Rec., 1922, xxiii, 17–18.

8. Evans, H. M., and Bishop, Katherine S.: Œstrus and ovulation in the rat from a large group of animals on a standard diet. Anat. Rec., 1922, xxiii, 18–19.

9. Fraenkel, L.: Vergleichend histologische Untersuchungen über das Vorkommen drüsiger Formationen im interstitiellen Eierstocksgewebe (glande interstitielle de l'ovaire). Arch. f. Gynaek., 1905, lxxv, 443–507.

10. Haldeman, K. O.: The method of opening of the vagina in the rat. Anat. Rec., 1921, xxi, 60.

11. Hatai, S.: On the weights of the abdominal and the thoracic viscera, the sex glands, ductless glands and eyeballs of the albino rat (mus norvegicus albinus) according to body weight. Am. Jour. Anat., 1913–1914, xv, 87–119.

12. Hatai, S.: The effect of castration, spaying or semi-spaying on the weight of the central nervous system and of the hypophysis of the albino rat; also the effect of semi-spaying on the remaining ovary. Jour. Exper. Zoöl., 1913, xv, 297–314.

13. Hatai, S.: The growth of organs in the albino rat as affected by gonadectomy. Jour. Exper. Zoöl., 1915, xviii, 1–67.

14. Heape, W.: Ovulation and degeneration of ova in the rabbit. Proc. Roy. Soc. London, 1905, lxxvi, series B, 260.

15. Jackson, C. M.: Postnatal growth and variability of the body and of the various organs in the albino rat. Am. Jour. Anat., 1913–1914, xv, 1–68.

16. Kingery, H. M.: So-called parthenogenesis in the white mouse. Biol. Bull., 1914, xxvii, 240–258.

17. Kingery, H. M.: Oögenesis in the white mouse. Jour. Morphol., 1917, xxx, 261–315.

18. Kingsbury, B. F.: The morphogenesis of the mammalian ovary (Felis domestica). Am. Jour. Anat., 1913, xv, 345–379.

19. Kingsbury, B. F.: The interstitial cells of the mammalian ovary: felis domestica. Am. Jour. Anat., 1914, xvi, 59–96.

20. Kirkham, W. B.: Ovulation in mammals with special reference to the mouse and rat. Biol. Bull., 1910, xviii, 245–251.

21. Kirkham, W. B., and Burr, H. S.: The breeding habits, maturation of the eggs and ovulation of the albino rat. Am. Jour. Anat., 1913, xv, 291–317.

22. Lane-Claypon, J.: On ovogenesis and the formation of the interstitial cells of the ovary. Jour. Obst. and Gynec. of British Empire, 1907, xi, 205.

23. Long, J. A., and Evans, H. M.: On the production of deciduomata during lactation. Anat. Rec., 1921, xxi, 58–60.

24. Long, J. A., and Evans, H. M.: On the rapid maturation of the ovary by transplantation of the youthful gonad to adults. Anat. Rec., 1921, xxi, 60.

25. Long, J. A., and Evans, H. M.: The œstrus cycle in the rat. Anat. Rec., 1920, xviii, 241–244.

26. Long, J. A., and Evans, H. M.: On the attainment of sexual maturity and the character of the first œstrus cycle in the rat. Anat. Rec., 1920, xviii, 244–245.

27. Marshall, F. H. A.: The physiology of reproduction. London, Longmans, 1910, 723 pp.

28. Morau, H.: Des transformations épithéliales de la muqueuse du vagin de quelques rongeurs. Jour. d. l'anat. et physiol., 1889, xxv, 277–297.

29. Robinson, A.: The formation, rupture, and closure of ovarian follicles in ferrets and ferret pole cat hybrids and some associated phenomena. Tr. Roy. Soc. Edinburgh, 1918, lii, 303.

30. Scammon, R. E.: Some peculiarities of the growth of the human uterus. Anat. Rec., 1919, xvi, 163.

31. Schaeffer, Anna: Vergleichend-histologische Untersuchungen über die interstitielle Eierstocksdrüse. Arch. f. Gynaek., 1911, xciv, 491.

32. Stockard, C. R., and Papanicolaou, G. N.: The existence of a typical œstrous cycle in the guinea pig with a study of its histological and physiological changes. Am. Jour. Anat., 1917, xxii, 225–283.

33. Valberg, M.: [A study of the anatomy of the ovaries in rabbits according to age.] Upsala Läkaref. Förh., 1914–1915, n. f., 169–242.

34. Winiwarter, H. v., and Sainmont, G.: Ueber die ausschliesslich postfœtale Bildung der definitiven Eier bei der Katze. Anat. Anz., 1908, xxxii, 613–616.

35. Winiwarter, H. v., and Sainmont, G.: Nouvelles recherches sur l'ovogenèse et l'organogenese de l'ovaire des mammifères. Arch. d. Biol., 1909, xxiv, 1–276.

no 17
759

THE GLANDULAR STATUS OF BROWN MULTIOCULAR ADIPOSE TISSUE

A. T. RASMUSSEN
Department of Anatomy
Medical School, University of Minnesota
MINNEAPOLIS

Reprinted from
ENDOCRINOLOGY
The Bulletin of the Association for the Study of Internal Secretions, 1100-1103 Title Insurance Bldg., Los Angeles, California, November, 1922, Vol. VI, No. 6, Pages 760 to 770.

THE GLANDULAR STATUS OF BROWN MULTILOCULAR ADIPOSE TISSUE

A. T. RASMUSSEN

Department of Anatomy, Medical School, University of Minnesota,

MINNEAPOLIS

This review seems justified by the fact that the brownish-colored and gland-like multilocular adipose tissue found in many mammals has repeatedly been considered to be an incretory gland and by the further fact that recently it has been suggested that it may be of importance in connection with deficiency diseases.

NAMES BY WHICH IT HAS BEEN KNOWN

While this multilocular adipose tissue is most often termed the *hibernating gland* (Barkow), it is met with in the literature under a variety of other names—*adipose gland* (Rudolphi), *oil gland* (Jones), *brown fat* (Hammar), *lipoid* or *cholesterin gland* (Cramer), *organ of hibernation* (von Hansemann), and *hibernating mass* (Vignes). A circumscribed fat mass in human foetuses in the dorso-cervical and interscapular regions, which some consider a homologous structure, has been called the *interscapular gland* by Hatai. As will be evident from the following discussion, there is very little and frequently no justification for many of these terms. The safest designation at the present time would seem to be *multilocular adipose tissue.*

GENERAL STRUCTURE AND COMPOSITION

In gross appearance it resembles very much a lobulated gland such as a salivary gland. Its fatty character is not suspected till examined microscopically. It consists of densely packed cells, 25 to 30 micra in diameter, whose cytoplasm is greatly distended with fat globules. These cells are bound together to a large extent by an unusually close plexus of capillaries. It differs from ordinary adipose tissue in that the essential cells are multilocular, much richer in granular cytoplasm and smaller in size. The nucleus remains spherical and, while frequently very eccentric in position, is never flattened against the margin. Carlier and Evans (1903) could obtain only 40 per cent of fat by weight from this tissue in the case of the hedgehog as compared with a yield of 90 per cent often obtainable from ordinary adipose tissue. As might be expected, they found as high as 15 to 16 per cent protein in the hibernating gland. Shattock (1909) reports that the iodine value of the fat differs in the two types of adipose tissue. According to Vignes (1913) the fatty material in the hibernating gland of the rat is composed largely of a substance closely related to lecithin, probably jecorin. Cramer (1920) also stresses the presence of considerable cholesterin and other lipoids, and yet Carlier and Evans (1903) found in the hedgehog that nine-tenths of the fat in the hibernating gland was olein, the remainder being sterin with a trace of palmitin, lecithin and pigment. The greater amount of pigment in the multilocular fat may play some rôle in preserving the unsaturation equilibrium of the fats, as suggested by Currie (1922). Although Carlier and Evans also made determinations on the mineral content and the solubility of the fat, the chemistry of this tissue is too meager to warrant any general conclusions.

In hibernating animals the amount of fat present and hence the size of the cells and the whole structure vary with the season of the year. It is maximum just before the onset of dormancy. It decreases slowly during winter-sleep and then more rapidly in the spring as the animal becomes active. The whole tissue is thus reduced to about one-fourth of its former bulk. It also becomes much darker in color. The cells decrease from 30 micra in diameter to 10 micra. In this reduced condition the cells resemble epithelial cells with an abundant granular cytoplasm in which is an occasional fat globule. There is no evidence that any cells revert to fixed connective tissue cells. The nucleus remains spherical in shape and unchanged in size. As summer advances the cells become filled with fat again, the tissue becomes lighter in color, and returns to its former size.

While nerves have been described in the organ, especially by Carlier (1893), no nerve supply to the essential cells has been positively demonstrated. (For further details the reader is referred to a forthcoming publication on the hibernating gland to appear in the Journal of Morphology, Philadelphia.)

LOCATION AND DISTRIBUTION

Usually there is a large mass of this tissue in the superior mediastinum, about the thymus. Numerous small masses extend upward along the large vessels of the neck and in the intermuscular septa of the cervical region. By means of slender prolongations dorsal to the clavicle, the cervical portion is frequently continuous with a prominent lobe in each axillary fossa. These latter lobes may represent one-half of the entire organ. A pair of lobes is often found between the scapulae and extending forward between the dorsal muscles of the neck. From the mediastinal mass there are slender caudal extensions along each sympathetic chain, aorta, and mammary arteries. In some animals it may extend into the abdominal cavity and form two prominent perirenal lobes. Less frequently isolated masses are found lower down along the aorta and its main branches as far as the inguinal region.

Examination of the literature reveals the fact that it has been found in about 47 species (5 insectivora, 9 chiroptera, 33 rodentia), with some uncertainty in several more species. Since most of them are hibernating animals, the association of this structure with winter-sleep has been repeatedly made; but there is a large number of species (rats, mice, rabbits, etc.) that possess this structure and yet do not hibernate. On the other hand, the organ is not found in some mammals that do hibernate (e. g., European badger).

The locations most often mentioned are the thoracic and cervical. Next in order come the axillary and interscapular. It is still less often indicated in the renal, while the inguinal is least often the site.

ITS HOMOLOGY IN MAN

Rather distinct circumscribed fat masses in the posterior triangle of the neck and axillary and interscapular regions have been described in some detail by Merkel (1899), Charpy (1901), Hatai (1902), Bonnot (1908) and Shattock (1909). Hatai, Bonnot and Shattock consider these to be probably homologous to the hibernating gland of lower forms. Shattock believes that the fatty swellings in the neck and axilla of cretins are the same structures as the hibernating gland which he found in these locations in the hedgehog. These fatty masses in thyroid disorders had been noted previous to this by T. B. Curling (1850) and again by H. Fagge (1871). Cramer (1920) stresses the glandular character of the perirenal fat, which, in the human embryo, appears to him to be essentially like the hibernating gland. But the literature does not present convincing proof of the similarity in structure between these fat masses and the typical hibernating gland. There is also some negative evidence. Berg (1910), who made an extensive examination of human material, Batty Shaw (1902) and Auerbach (1902) were unable to see anything in man that resembled the brown fat of animals.

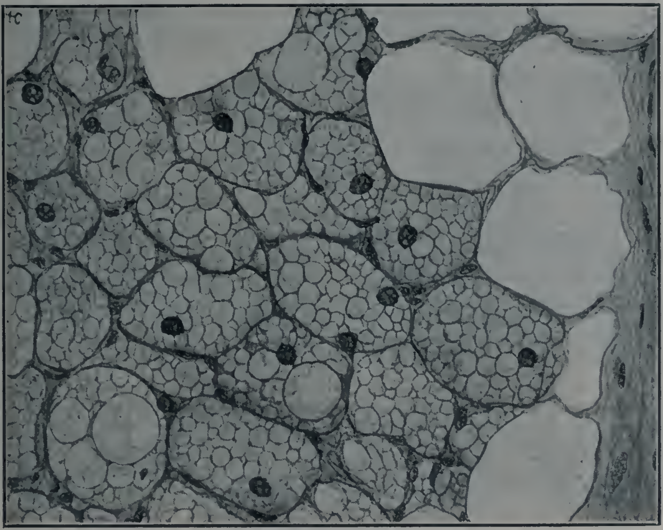


Fig. 1. Camera lucida drawing of multilocular fat cells and a few ordinary adipose tissue cells from the perirenal fat of a normal newborn child. Formalin fixation; celloidin; hematoxylin and eosin. X 400. By comparing this figure with Fig. 2 the similarity in structure between these multilocular fat cells and the essential cells of the so-called hibernating gland of animals is clearly evident.

In spite of the above negations, there are occasionally in the perirenal fat of newborn and very young children cells, as shown in Figure 1, which are in all structural details essentially the same as the typical hibernating gland cells (Fig. 2). Just how often and how widespread such multilocular fat cells may be found in man no one can say for lack of sufficiently extensive examination of human material. The cells here shown in Figure 1 are not developmental stages of ordinary fat, for in the latter case the nucleus is early crowded and flattened against the cell margin and the droplets coalesce into a larger and larger globule which fills most of the cell long before it reaches the size of those illustrated here. The relatively large amount of cytoplasm is also atypical of ordinary developing adipose tissue. Then, too, no intermediate stages are clearly seen.

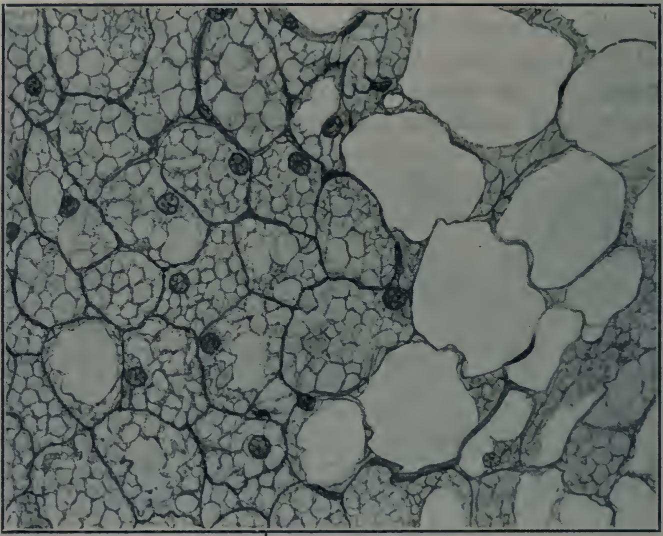


Fig. 2. Camera lucida drawing of the brown fat or hibernating gland cells and a few ordinary adipose tissue cells from the common white rat. The relative abundance and multilocular character of the cytoplasm as well as the spherical shape of the nucleus in hibernating gland cells are well contrasted with the general appearance of the adjacent cells of ordinary adipose tissue. Except for greater shrinkage (due to paraffin embedding) this figure is strikingly similar to Fig. 1, which is from a human subject.

DEVELOPMENT

Carlier (1893) describes these hibernating gland cells in the hedgehog as coming from small round granular connective tissue cells, similar to those that give origin to ordinary fat cells. Hammar (1895) found the anlage of the interscapular lobe in the rat first to differentiate from the mesenchyme in embryos 1.2 cm. in length; but fat droplets did not appear till the latter part of intrauterine life, when it accumulated rapidly. He was unable by feeding rats for three months on a diet rich in fat to change these cells into ordinary adipose cells. There always remained the wide cytoplasmic border. Von Hansemann, who also utilized the rat, found the first trace of these multilocular fat cells in foetuses 1.6 cm. in length in both the dorsal region of the neck and the axilla. Later it appeared in the neighborhood of the thymus. The cells first appear as large polygonal cells of connective tissue origin. Large blood vessels are associated with these cells before they have differentiated. Both the place of development and the histogenesis, he claims, distinguish this brown glandular fat from ordinary adipose tissue. Bonnot (1908) described the "interscapular gland" in human subjects as arising from the walls of the primitive jugular vein. The tissue which forms in this region differentiates into lymphoid tissue and fatty lobules. The lymphoid tissue in turn develops into lymph nodes and hemolymph nodes. There seems to be no justification, however, for considering the lymph nodes as part of this fatty structure.

FUNCTIONAL SIGNIFICANCE

This gland-like adipose tissue was first mentioned by Velsch in 1670. He thought it was of a lymphatic nature and functionally related to the thymus. The next three writers on the subject (Harder, 1686; Scheuczer, 1727; Buffon, 1749) make no comment on its function. Sulzer (1774) spoke of it as a gland; Pallas (1778), Meckel (1806, 1815), Mangili (1807), Prunelle (1811), and Tiedemann (1815) considered it a part of the thymus.

It was Ludwig Jacobson who, in 1817, first clearly showed that it is a distinct structure and not a part of the thymus. He demonstrated that in marmots, hedgehogs and bats the thymus undergoes the usual involution and in its place develops a fatty tissue which varies in size with the season of the year. This work was repeated by Haugstedt (1831), who fully corroborated the findings of Jacobson. Rudolphi (1830) and Wagner (1835) similarly considered it as only a modified form of adipose tissue; but Burdach (1830), Simon (1845) and Jones (1852) adhered to the old notion that it was a persistent thymus, although Simon recognized that it may become changed to a mass of fat cells.

Barkow (1846) was the first to call it the hibernating gland. Although he recognized that it was a separate organ from the thymus, he considered that it belonged with the ductless glands such as the thymus, thyroid, etc. That it is a separate structure from the thymus, but still a ductless gland probably of the haemopoietic series, was also the belief of Ecker (1853), Valentine (1857, 1859), Leydig (1857), Friedleben (1858), Vogt and Yung (1894) and Wiedersheim (as late as 1907).

Stannius (1853) had the peculiar notion that the sympathetic nervous system developed from its interior.

Beginning with Hirsel and Frey in 1863, the hibernating gland has in general been regarded as a variety of adipose tissue probably serving merely as a source of food during winter-sleep. From histological studies, Hirsel and Frey decided that there is no similarity between this fatty tissue and lymph- or blood-forming organs in general and the thymus in particular, although their idea of the finer structure was entirely erroneous. Sharing very much this same idea of its functional significance are Owen (1868), Fleischel (1869), Afanassiew (1877), Ehrmann (1883), Poljakoff (1888), Carlier (1893), Hammar (1895), Dubois (1896), von Hansemann (1902), Auerbach (1902) and Polimanti (1912). Polimanti suggests that it may also act as a protective cushion enveloping the thorax and thus guarding the internal organs from the external temperature.

Its importance as a special source of food for the hibernating period has, however, been greatly overestimated, at least as far as the amount of material that it yields is concerned, as is evident especially from the figures given by Valentine (1857, 1859). This investigator found that the hibernating gland of the European marmot, while giving up nearly 70 per cent of its weight as food during winter-sleep, represents, to begin with, only 1.33 per cent of the total body weight. Calculations from his figures show that ordinary adipose tissue contributed 20 times as much material during the same time and skeletal muscle 8 times as much and the liver 2 times as much as the hibernating gland. Since other tissues also yield food material it follows that less than one-thirtieth of the consumed body tissues came from the hibernating gland. Carlier (1893) gives somewhat higher figures for the hedgehog, in which the structure represents about 3 per cent of the body weight before hibernation and decreases during dormancy to about 1 per cent.

A number of other investigators (Aeby, 1875; Harvath, 1878, and Ballowitz, 1891) of this period do not commit themselves on the physiological phase of the question.

Although the notion that the hibernating gland is a persistent thymus and the later idea that it is a separate organ but still of the haemopoietic series were discarded, the theory that it is a gland of some sort persisted. Thus Malesani (1902) was struck with its glandular appearance and considered it to be a ductless gland which was of great importance during hibernation. Shattock (1909), because of the discrete droplets of lipoid which its cells contain, thinks it is allied to the ductless gland, and since it does not behave like ordinary adipose tissue (being spared during the major portion of the dormant period) it is physiologically as well as histologically specialized. Salmon (1910, 1916) argues that it is the only organ that is active during winter-sleep and functions as a true endocrine organ by inhibiting all other glands of internal secretion.

Vignes (1913), from the experiments reviewed in the next section of this paper, concluded that the organ may be considered an economizer of proteins by insuring the utilization of reserved carbohydrates and fats first. This suggestion is interesting in connection with more recent work on the rôle of ordinary fats in the utilization of proteins by diminishing their toxicity and increasing their availability, as argued by Maignon (1921).

Finally Cramer (1920) lays stress upon the fact that the fatty material is rich in cholesterin compounds and other lipoids and that this lipoid is retained during ordinary starvation, but is used up in animals dying for lack of accessory food factors. He suggests that the lipoid has been used up to supply vitamines. From the great similarity in the reaction to polarized light between the suprarenal cortex and this multilocular fat, he assumes that there is also great similarity in composition.

EXTIRPATION EXPERIMENTS

Apparently the first extirpation experiments on record in connection with this multilocular fat tissue are those by Dubois (1896), who first merely exposed the structure in the marmot to see the effects of the necessary preliminary operative procedure. On the following day as much of the tissue as possible was removed. Two of the animals lived two or three days and during this time they exhibited no difficulty in warming up rapidly after torpor.

Auerbach (1902) extirpated the dorsal part of the hibernating gland in a rat. The animal lived two months. There was no regeneration of the lost tissue, its place being occupied by ordinary adipose tissue.

As the results of an extensive series of extirpation experiments in connection with the utilization of extracts of the hibernating gland on white rats and mice, Vignes (1913) found that while most of the rats survived the removal of a large part of the organ (it is improbable that complete removal could be achieved) they lost weight and finally died. Only two lived more than three months. One lived four and one-half months. In the mouse, in which the operation is more difficult, the animals survived indefinitely, although there was an initial loss of weight. The rats operated upon had an increased resistance to adrenalin and cobra venom and a lessened resistance to chloroform. He also found that the extract of this fatty tissue increased the toxic power of tetanus toxin. The organ also apparently modified enzyme action for its extirpation diminished the quantity of lipase in the serum of the rats. It contained a lipase which acted on monobutyrin. The amyloptic power of the serum of the experimental rats was diminished; but extracts of the organ did not act on starch. The extract had an antitryptic power since it inhibited the action of trypsin. Vignes suggests that further studies on this organ would increase our understanding of the rôle of the phosphatides in metabolism. His conclusions have already been stated.

CONCLUSIONS

The brown multilocular adipose tissue, most commonly termed the hibernating gland, but known also by a variety of other terms, seems to be found mostly in rodents, but also in a few species of insectivora and chiroptera. A few similar cells are found occasionally in the perirenal fat of young children and newborn, but certainly there is no good evidence that the masses of fatty tissue described in other regions of the human body should be considered homologous to the hibernating gland of animals. It is not confined to hibernating mammals, nor is it present in all mammals that pass the winter largely in a dormant condition.

It is clearly evident that no one has gone extensively enough into the physiological significance of this brown multilocular adipose tissue to justify its classification as a gland. The granular character of the cytoplasm, the presence of numerous discrete fatty globules and other structural features of this tissue are not sufficient criteria by which to judge its glandular properties. The prevailing opinion during the past 50 or 60 years has been that it is merely one type of adipose tissue. The best designation for this tissue at the present time would seem to be multilocular adipose tissue.

Its importance as a special source of food for the hibernating period has been overestimated, at least as far as bulk is concerned, yielding as it does only about one-thirtieth of the body tissues consumed in the case of the common European marmot (a slightly higher yield in the American marmot is indicated by figures to be published by the writer in the Journal of Morphology), and about one-fifteenth in the case of the hedgehog.

Extirpation experiments are of little value on account of the extensive distribution of the tissue. The effects of its extracts have been investigated practically by only a single worker (Vignes), who believes he has evidence from enzyme action that it functions as a protein sparer during winter sleep. The latest theory, that it may be a special source of vitamines, is based on such meager data that it need not be taken seriously.

BIBLIOGRAPHY

Aeby, C.: 1875. Arch. f. exper. Path. u. Pharmakol (Leipzig), **3**, 180.
Afanássiew, B.: 1877. Arch. f. mikr. Anat. (Bonn), **14**, 375.
Auerbach, M.: 1902. Arch. f. mikr. Anat. (Bonn), **60**, 291.
Ballowitz, E.: 1901. Anat. Anz. (Jena), **6**, 135.
Barkow, H. C. L.: 1846. Der Winterschlaf nach seinen Ercheinungen im Thierreich dargestellt. (Berlin), chap. 16.
Berg, W.: 1910-11. Ztschr. f. Morph. u. Anthrop. (Stuttgart), **13**, 305.
Bonnot, E.: 1908. J. Anat. & Physiol. (London), **43**, 43.
Buffon, G. L. L.: 1749. Oeuvres avec des suppléments augmentées de la classification de G. Cuvier. (Paris, 1835), **5**, 226.
Burdach, K. F.: 1830. Die Physiologie als Erfahrungswissenschaft. (Leipzig), **3**, 510.
Carlier, E. W.: 1892-93. J. Anat. & Physiol. (London), **27**, 508.
Carlier, E. W., & Evans, C. A. L.: 1903-04. J. Anat. & Physiol. (London), **38**, 15.
Charpy, A.: 1901. Traité d'anatomie humaine (Poirier-Charpy) (Paris), **2**, 427.
——: 1907. Bibliographie anatomique (Paris & Nancy), **16**, 207.
Cramer, W.: 1920. Brit. J. Exper. Path. (London), **1**, 184.
Curling, T. B.: 1850. Med.-Chir. Trans. (London), **33**, 303.
Currie, A. N.: 1922. J. Path. & Bacteriol. (Edinburgh), **25**, 213.
Dubois, R.: 1896. Physiologie Comparée. (Paris), pp. 225 and 94.
Ecker, A.: 1853. Wagner's Handwörterbuch der Physiologie. (Braunschweig), **4**, 121.
Ehrmann, S.: 1883. Sitzungsb. d. k. Akad. d. Wissensch., Math. Naturw. Classe, Abteil. 3 (Wien), **87**, 88.
Fagge, H.: 1871. Med.-Chir. Trans. (London), **54**, 154.
Fleisch, E.: 1869. Sitzungsb. d. k. Akad. d. Wissensch., Math. Naturw. Classe, Abteil. 2 (Wien), **60**, 60.
Friedleben, A.: 1858. Die Physiologie der Thymusdrüse. (Frankfurt a. M.), Abschnitt 10, 102.
Hammar, J. A.: 1895. Arch. f. mikr. Anat. (Bonn), **46**, 512.
Hansemann, D. (von): 1902. Arch. f. Anat. u. Physiol., Physiol. Abt. (Leipzig), p. 160.
Harder, J. J.: 1686. Ephemerid. acad. nat. cur. Ann. 4, Dec. 2, obs. 122.
Hatai, S.: 1902. Anat. Anz. (Jena), **21**, 369.
Haugstedt, F. C.: 1831. Thymi in homine ac per seriem animalium descriptionis anatomico-physiologische particula prior. (Hauniae), **28**.

Hirzel, H., & Frey, H.: 1863. Ztschr. f. wissensch. Zool. (Leipzig), **12**, 165.

Horvath, A.: 1878-1881. Verhandl. d. phys. med. Gesellsch. (Würzburg), N. F., Bd. 12-15.

Jacobson, L.: 1817. Deut. Arch. f. d. Physiol. (Halle), **3**, 151.

Jones, C. H.: 1852. Todd's Cyclopaedia of Anat. and Physiol. (London), **4**, 1095.

Leydig, Fr.: 1857. Lehrbuch der Histologie. (Frankfurt a. M.), 431.

Maignon, F.: 1921. Arch. internat. de physiol. (Liége & Paris), **18**, 103.

Malesani, L.: 1902. (Cited by Salmon, La Fonction du Sommeil, p. 89).

Mangili, G.: 1807. Annales du muséum d'histoire naturelle. (Paris), **9**, 106.

Meckel, J. F.: 1806. Abhandl. aus der mensch. u. vergleich. Anat. u. Physiol. (Halle), **8**, 1.

——: 1815. Deutsch. (Meckel's) Arch. f. d. Physiol. (Halle), **1**, 493.

Merkel, F.: 1899. Topographische Anatomie. (Braunschweig), **2**, 27.

Mietens, H.: 1909. Jenaische Ztschr. f. Naturw. (Jena), **44**, 149 (especially pp. 171-176).

Owen, R.: 1868. On the Anatomy of Vertebrates. (London), **3**, 568.

Pallas, P. S.: 1778. Novae species quadrupedum e glirium ordine. (Erlangen).

Polimanti, O.: 1912. Il Letargo. (Roma), **46**.

Poljakoff, P.: 1888. Arch. f. mikr. Anat. (Bonn), **32**, 155.

Prunelle, C. F. V. G.: 1811. Annales du museum d'histoire naturelle. (Paris), **18**, 302.

Rudolphi, K. A.: 1830. Grundriss der Physiologie. (Berlin, Reutlingen, J. J. Mäcken'schen Buchhandlung), **1**, 244.

Salmon, A.: 1910. La Fonction du Sommeil. (Paris), pp. 88 and 163.

——: 1916. Lo Sperimentale (Florence), **70**, 345.

Scheuczer, J. J.: 1727. Phil. Trans. (London), **34**, 237; ibid., abridged by Eames & Martin, **7**, 453.

Shattock, S. G.: 1908-9. Proc. Roy. Soc. Med. (London), **2**, Part 3, Pathological Section, 207 (particularly p. 252).

Shaw, H. Batty: 1902. J. Anat. & Physiol. (London), **36**, 1.

Simon, J.: 1845. A Physiological Essay on the Thymus Gland. (London), **46**.

Stannius, H.: 1853. Beobachtungen über Verjungungsvorgänge im thierischen Organismus (Rostock and Schwerin).

Sulzer, F. G.: 1774. Versuch einer Naturgeschichte des Hamsters (Göttingen).

Tiedemann, F.: 1815. Deutsch. (Beckel's) Arch. f. d. Physiol. (Halle), **1**, 481.

Valentin, G.: 1857. Untersuchungen zur Naturlehre des Menschen und der Thiere (von Jac. Moleschott). (Frankfurt a. M.), **2**, 12; ibid., 1859, **5**, 259.

Velsch, G. H.: 1670. Ephemerid. acad. nat. cur. Ann. 1, Dec. 1, obs. 160, 298.

Vignes, H.: 1913. Compt. rend. Soc. de biol. (Paris), **75**, 360; 397; 418.

Vogt, C., & Yung, E.: 1889-1894. Lehrbuch der praktischen vergleichende Anatomie. (Braunschweig), **2**, 955.

Wagner, R.: 1834-35. Lehrbuch der vergleichenden Anatomie. (Leipzig), 253.

Wiedersheim, R.: 1907. Comparative Anatomy of Vertebrates, 3rd Ed. (founded on the sixth German edition, by W. N. Parker). (London), 435.

Reprinted from the Proceedings of the Society for Experimental Biology and Medicine,
1922, xx, pp. 104-107

no 18.
1

51 (2011)

Experimental demonstration of the entire course of four descending tracts[1] by a single alcoholic injection in the mid-brain of the cat.

By A. T. RASMUSSEN.

[*From the Department of Anatomy, Medical School, University of Minnesota, Minneapolis, Minnesota.*]

By trephining a hole 2 cm. in diameter, 1 cm. anterior to the occipital crest and 2 cm. from the median line, and retracting the occipital pole of the cerebral hemisphere of the cat, the superior colliculus was exposed and about two drops of 95 per cent. alcohol injected into the nucleus ruber with a fine hypodermic syringe. The needle should enter the surface at about the middle of the colliculus and be directed slightly medially and at right angles to the long axis of the brain stem to a depth of 1 cm. After the usual two weeks, the animal was killed and the brain carried through the regular Marchi method.

As the accompanying illustrations show, it is possible in this manner to cause degeneration of the entire extent of four descending tracts, two of which are not easily recognizable on normal material and yet are functionally of great importance. These fiber bundles in the cat are situated in the same relative position as in man.

Although the exact course (especially peripherally) of the mesencephalic root of the trigeminal nerve has been much debated[2], it is clearly evident that its exit through the pons is closely associated with the motor root of the trigeminal nerve.

---

[1] Fasciculus longitudinalis medialis, fasciculus tectospinalis, fasciculus rubrospinalis, radix mesencephalica trigemini.

The fibers from the nucleus of the medial longitudinal fasciculus (degenerated only on one side) and those from the tectum mesencephali (degenerated mostly on the contralateral side) occupy distinct regions throughout their entire course in the cat. Numerous other experiments in which we have limited the lesion to the tectum of the mid-brain have failed to show that any fibers from this region enter what is strictly the medial longitudinal fasciculus. The lower termination of the tectospinal fasciculus has been variously given[3]. In this and the other experiments referred to above, fibers of this fasciculus cannot be followed farther than the upper part of the 7th cervical segment. It is very probable that the fibers followed below this level by others belong to some other tract such as the medial longitudinal fasciculus, which extends throughout most of the spinal cord. It is the large number of ascending and descending fibers from the vestibular nuclei that make it appear that the medial longitudinal fasciculus is partly mixed with the tectospinal. A clearer designation of the various fiber tracts now generally considered as part of the medial longitudinal fasciculus is highly desirable.

The rubrospinal fasciculus, from its origin, size and extent, as well as from clinical studies[4], should be regarded as an important motor pathway by which both the corpus striatum and cerebellum may exert its influence on lower motor centers. While widely separated from the pyramidal tract above the pyramidal decussation, below this point it is more and more closely associated with the lateral (crossed) pyramidal tract. As was to be expected, the physiological effects of the injection of one nucleus ruber was much the same as a large lesion in the opposite cerebellar hemisphere.

---

[2] Allen, W. F., *Jour. Comp. Neur.*, 1919, xxx, 169.

[3] Collier, J. and Buzzard, F., *Brain*, 1901, xxiv, 177.

[4] Hunt, J. R., *Jour. Nerv. and Ment. Dis.*, 1916, xliv, 437; 1917, xlvi, 211; *Brain*, 1918, xli, 302.

AUTHOR'S ABSTRACT OF THIS PAPER ISSUED
BY THE BIBLIOGRAPHIC SERVICE, SEPTEMBER 10

Reprinted from JOURNAL OF MORPHOLOGY
Vol. 38, No. 1, September, 1923

n° 19

THE SO-CALLED HIBERNATING GLAND

A. T. RASMUSSEN
Medical School, University of Minnesota, Minneapolis

EIGHT PLATES (NINETEEN FIGURES)

CONTENTS

Introduction 147
Gross and microscopic structure 148
General location and distribution 150
Is there a homologous structure in man? 162
Development 167
Functional significance 170
The hibernating gland of the woodchuck 174
  Position and relations of lobes 175
  Microscopic structure 178
  Changes during and subsequent to hibernation 180
Comparison with ordinary adipose tissue 186
Summary 189
Bibliography 192

INTRODUCTION

The recent suggestion (Cramer, '20) that the gland-like adipose tissue, met with in the literature under a number of different names [adipose gland (Rudolphi, '30), brown adipose tissue (Hammar, '95—although some previous writers spoke of it as brown colored fat), oil gland (Jones, '52), lipoid or cholesterin gland (Cramer, '20), interscapular gland (Hatai, '02), organ of hibernation (von Hansemann, '02), hibernating mass (Vignes, '13), hibernating gland (Barkow, '46)], will have to be considered as a factor in the etiology of deficiency diseases, would seem to justify a rather thorough consideration of this structure. Ever since its discovery by Velsch in 1670 it has repeately been either confused with the thymus or considered as a separate ductless gland. For a period of about forty years after being recognized as distinct from the thymus it was generally classified as a ductless gland of the hemopoietic series.

The fallacy as to its hemopoietic character was proved many years ago; but several times in the last twenty years evidence has been presented to show that it is a ductless gland of some importance.

Since in modern text-books there is almost a total lack of information, even on the structure of this tissue, and because of the fact that there is no recent extensive review of the literature in English, an examination of the views regarding its morphology and significance expressed by the numerous men who have given it some attention is highly desirable.

The hibernating gland of the American marmot (woodchuck) is utilized as illustrative material largely because a detailed account of it in our North American species has not been found. Bonnot ('08) merely makes mention of it and Cushing and Goetsch ('15) only incidentally made some observations on seven specimens, but these were fragmentary and upon tissue not specifically fixed for preservation of the fat so that little dependence can be placed upon their description. The writer has worked for a number of years with one of the species (Marmota monax rufescens), in which there is a typical and well developed hibernating gland upon which general observations have been made in about 120 cases during the course of four years. Material for histological study was taken from 52 of them. A limited amount of material from the white rats and human subjects was investigated to check a few debated points.

The work was commenced at the suggestion of Dr. A. T. Kerr of Cornell University. Credit is also due Dr. C. M. Jackson for many valuable suggestions.

GROSS AND MICROSCOPIC STRUCTURE

The typical hibernating gland is light brown in color and has many glandular features from external appearances largely because of its lobulated character, which is due to loose fibrous connective tissue septa dividing it into irregular units (fig. 6). Except for its darker color, the mediastinal portion might easily be mistaken for the thymus if one were unaware of the presence of this special adipose tissue. Scheuczer (1727) spoke of *glands* *located among the muscles* in the marmot, evidently with reference to the hibernating gland (see especially fig. 3), while Buffon (1749), also in connection with the European marmot, said it resembled the mammary gland of the cow. Larger blood vessels, a few nerve fibers and a variable amount of ordinary adipose tissue are usually found in these connective tissue septa. A thin fibrous capsule and in places ordinary adipose tissue mark its limits nicely from the surrounding structures.

While Harder as early as 1686 noted that this tissue yielded a fatty juice and Jacobson in 1817 clearly showed that it was not a lymphatic tissue but structurally a form of adipose tissue, the first good and essentially correct histological description was made by Ecker in 1853, who illustrated the finer structure of the parenchyma by material obtained from the hedgehog and bat. In 1863 Hirsel and Frey, after examining tissue from six different species, published an entirely erroneous description, except for the rich blood supply which they demonstrated beautifully by means of vascular injection. Afanassiew ('77), Ehrmann ('83), Carlier ('93), Hammar ('95), von Hansemann ('02), Auerbach ('02), Shattock ('09), Cramer ('20) and some others have made observations on various animals with some further advance in our knowledge. From these results as well as the investigations reported here, it is clear that the parenchyma is composed of densely packed polygonal cells about 25 to 30μ in diameter, with rather abundant and highly granular cytoplasm in which there are usually a large number of fat globules of various sizes. The large spherical nucleus is rarely, if ever, flattened although it may be pushed to the cell margin (fig. 12). Auerbach ('02), from a study of 102 animals belonging to 26 different species, found these cells extraordinarily uniform in structure in different species. He, like Hammar ('95), could not demonstrate the cell wall that some of the previous workers mentioned. Hammar thought he saw evidences of intercellular bridges at certain points. The intercellular space is occupied by a very rich plexus of blood capillaries (fig. 11).

Carlier ('93), whose extensive observations were carried out on the hedgehog, described in considerable detail the nerve supply to the various lobes, but the relation of these nerves to the parenchyma cells has never been demonstrated. Carlier found a nerve ganglion consisting of small pyriform cells in an axillary lobe and was able to demonstrate a plexus of non-medullated nerve fibers in the arteries of this organ.

Ballowitz ('91) made a special study of the mast cells of Ehrlich in bats during winter-sleep and found only a few in the hibernating gland, but these were not modified in structure or number by the prolonged inanition incident to dormancy.

Various inclusions were described by Ehrmann ('83), among which were closed follicles surrounded by connective tissue membranes and filled either with granular debris or a homogeneous mass resembling the colloid of the thyroid; but since they were found in the cervical region near the thyroid gland, they were evidently accessory thyroids. Lymph nodes are frequently present (figs. 6 and 7), but there is no justification for the contention of Bonnot ('08) that such lymph nodes are an essential part of the hibernating gland proper.

GENERAL LOCATION AND DISTRIBUTION

The position of the hibernating gland is quite characteristic. There is a large mass in the superior mediastinum about the atrophied thymus (fig. 1). From this thoracic portion there are extensions into the intermuscular septa of the cervical region where many small and more or less detached portions are widely distributed (fig. 2), with a large lobe in the lateral portion of the neck (fig. 3). By means of slender prolongations dorsal to the clavicles, the cervical portion is frequently continuous with a prominent lobe situated in each axillary fossa (fig. 5). There is usually a pair of dorsal lobes situated between the scapulae and extending cephalad along the muscles of the back of the neck. There are slender caudal extensions from the thoracic mass along each sympathetic nervous chain, along the lateral borders of the aorta and along the mammary artery (fig. 1). In many animals it may extend into the abdominal cavity where there is often a fairly prominent perirenal lobe. Less frequently isolated lobes are described lower in the abdominal cavity along the iliac vessels and near the inguinal region.

The name of the species in which the hibernating gland has been found, its location in the body, the authority therefore, etc., are found in the accompanying table, part of which was originally compiled by Auerbach ('02, pp. 324–328), then slightly added to by Polimanti ('12, pp. 50–54) and finally extended and modified by the writer where an examination of the original literature seemed to justify the changes. The names of the species have been brought up to date, but older names and common names are included in order to facilitate checking with the original sources and in other ways increasing the value of the tables. The list has been carefully corrected by the Bureau of Biological Survey (U. S. Dept. of Agriculture, Washington, D.C.), E. W. Nelson, Chief of Bureau, to whom the author is greatly indebted.

An examination of this table shows that the locations most often mentioned as containing hibernating gland tissue are the thoracic and cervical. Next in order come the axillary and scapular regions. It is still less often mentioned in the renal; while the inguinal location is least often the site, being mentioned only about one-fourth as many times as the thoracic. The data are, however, not reliable in this regard because many authors have only incidentally noted the presence of this structure and have not looked carefully for its distribution. Naturally it would be noticed first in the thoracic and lower cervical regions on account of its presenting the appearance of a persistent thymus. But it is safe to say that it is not always present in the abdominal cavity and especially in the inguinal region when it is present in all the other places.

It will be seen from the table that in the Norway rat von Hansemann ('02) denies the existence of any part of the hibernating gland in the inguinal region, while both Hammar ('95) and Auerbach (02) considers it present. Mietens ('08) also mentions multilocular fat cells in this location in both rats and white mice. This disagreement among comparatively recent investigators in connection with such a common species seems strange. Von Hansemann admits that there is a rather dark colored adipose tissue in this position in the rat, but this, he says,

SPECIES	AUTHOR	+ = PRESENT, — = ABSENT						REMARKS
		Cervical	Scapular	Axillary	Thoracic	Renal	Inguinal	
Insectivora								
Erinaceus europaeus (hedgehog)	Prunelle	?	?	?	+	?	?	Only thoracic mentioned
Erinaceus europaeus (hedgehog)	Tiedemann	?	?	?	+	?	?	Distribution not given
Erinaceus europaeus (hedgehog)	Meckel	+	+	+	+	?	?	4 specimens examined
Erinaceus europaeus (hedgehog)	Jacobson	?	?	?	+	?	?	Distribution not given
Erinaceus europaeus (hedgehog)	Simon	—	—	—	—	—	—	
Erinaceus europaeus (hedgehog)	Jones	+	?	+	—	?	?	2 specimens, end of hibernation
Erinaceus europaeus (hedgehog)	Ecker	+	+	+	+	?	?	At least recognized these four portions
Erinaceus europaeus (hedgehog)	Hirzel and Frey	?	?	?	?	?	?	Distribution not given
Erinaceus europaeus (hedgehog)	Afanassiew	+	+	+	+	?	?	In locations given by Barkow
Erinaceus europaeus (hedgehog)	Ehrmann	+	?	?	+	?	?	Complete location not given
Erinaceus europaeus (hedgehog)	Carlier	+	+	+	+	—	—	Numerous specimens
Erinaceus europaeus (hedgehog)	von Hansemann	?	+	?	?	?	?	Scapular specially mentioned
Erinaceus europaeus (hedgehog)	Auerbach	+	+	+	+	±	±	6 specimens examined
Erinaceus europaeus (hedgehog)	Shattock	+	+	+	+	—	—	Corroborates Carlier
Erinaceus europaeus (hedgehog)	Polimanti	+	+	+	+	+	±	8 specimens examined
Hedgehog (species not given)	Cushing and Goetsch	—	—	—	—	—	—	3 specimens examined
Talpa europaea (mole)	Jacobson	?	?	?	+	?	?	Distribution not given, fairly well developed
Talpa europaea (mole)	Simon	—	—	—	—	—	—	
Talpa europaea (?)	Jones	—	—	—	—	—	—	Existence definitely denied
Talpa europaea	Auerbach	+	+	+	+	+	?	5 specimens examined
Talpa europaea	Polimanti	+	+	+	+	+	±	9 specimens examined

Talpa europaea	Vignes	?	?	?	?	?	?	Well developed, location not given
Sorex ("spitzmaus," shrew-mouse)	Jacobson	?	?	?	+	?	?	Distribution not given, fairly well developed
Sorex araneus (common shrew of England)	Simon	?	?	+	+	?	?	Axillary fat as in hibernating rodents
Sorex myosurus (Pachyura murina, a tropical species)	Simon	–	–	–	–	–	–	
Tupaia javanica	Simon	–	–	–	–	–	–	
Tupaia glis ferruginea (a squirrel-like animal)	Auerbach	?	?	?	?	?	?	Uncertain, poor preservation
Chiroptera (bats)								
Vespertilio murinus	Prunelle	?	?	?	+	?	?	Only thoracic mentioned
Vespertilio murinus	Ecker	+	+	+	+	?	?	At least recognized these four portions
Vespertilio murinus	Hirzel and Frey	?	?	?	?	?	?	Distribution not given
Vespertilio murinus	Polimanti	+	+	+	+	+	+	6 specimens examined
Vespertilio noctula	Polimanti	+	+	+	+	+	+	6 specimens examined
Plecotus auritus (Vespertilio auritus)	Hirzel and Frey	?	?	?	?	?	?	Presence merely noted
Plecotus auritus (Vespertilio auritus)	Polimanti	+	+	+	+	+	+	6 specimens examined
Myotis mystacinus (Vespertilio mystacinus	Auerbach	+	+	+	+	+	–	2 specimens examined
Myotis mystacinus (Vespertilio mystacinus	Polimanti	+	+	+	+	+	–	6 specimens examined
Vespertilio (several species but names not given)	Simon	+	?	?	+	?	?	Described as persistent thymus

SPECIES	AUTHOR	+ = PRESENT, — = ABSENT						REMARKS
		Cervical	Scapular	Axillary	Thoracic	Renal	Inguinal	
Pteropus vampyrus edulis	Simon	+	?	?	+	?	?	Described as persistent thymus
Galeopithecus	Simon	+	?	?	+	?	?	Described as persistent thymus
Cynopterus sphinx (Cynopterus marginatus Geoff.)	Auerbach	?	?	?	?	?	?	Uncertain, poor preservation
Rhinolophus affinis Horsfield	Auerbach	?	?	?	?	?	?	Uncertain, poor preservation
Species not given	Tiedemann	?	?	?	+	?	?	Distribution not given
Species not given	Meckel	+	?	+	+	?	?	2 specimens examined
Species not given	Jacobson	?	?	?	+	?	?	Distribution not given
Species not given	Jones	+	?	+	+	?	?	
"Native bats"	Wagner	+	?	+	+	?	?	
Species not given	Afanassiew	+	+	+	+	?	?	In locations given by Barkow
Species not given	Ehrmann	+	?	?	+	?	?	Complete location not given
Species not given	Ballowitz	?	?	?	?	?	?	Distribution not given
Rodentia								
Marmota marmota (Arctomys marmota, European marmot)	Velsch	?	?	?	+	?	?	Only thoracic portion mentioned
Marmota marmota (Arctomys marmota, European marmot)	Harder	+	+	?	+	?	?	Present in the abdomen
Marmota marmota (Arctomys marmota, European marmot)	Scheuczer	?	?	?	?	+	+	Also mentions intermuscular glands
Marmota marmota (Arctomys marmota, European marmot)	Buffon	?	+	?	?	+	?	
Marmota marmota (Arctomys marmota, European marmot)	Prunelle	?	?	?	+	+	+	Extends to iliac arteries

Marmota marmota (Arctomys marmota, European marmot)	Tiedemann	+	?	+	+	?	?	2 specimens examined
Marmota marmota (Arctomys marmota, European marmot)	Meckel	+	?	+	+	?	?	7 specimens examined
Marmota marmota (Arctomys marmota, European marmot)	Jacobson	?	?	?	+	?	?	Distribution not given
Marmota marmota (Arctomys marmota, European marmot)	Simon	+	?	+	+	?	?	4 specimens examined
Marmota marmota (Arctomys marmota, European marmot)	Ecker	+	+	+	+	?	?	Only thoracic specifically mentioned; but describes the other three portions
Marmota marmota (Arctomys marmota, European marmot)	Valentine	+	+	+	+	+	+	Extends to iliac arteries
Marmota marmota (Arctomys marmota, European marmot)	Hirzel and Frey	+	+	+	+	?	?	
Marmota marmota (Arctomys marmota, European marmot)	Afanassiew	+	+	+	+	?	?	In locations given by Barkow
Marmota marmota (Arctomys marmota, European marmot)	von Hansemann	?	+	?	?	?	?	Scapular specially mentioned
Marmota marmota (Arctomys marmota, European marmot)	Auerbach	+	+	+	+	+	+	2 specimens examined
Marmota marmota (Arctomys marmota, European marmot)	Polimanti	+	+	+	+	+	+	6 specimens examined
Marmota marmota (var. Russo-Asiatica)	Pallas	+	–	+	+	+	–	Cited by Auerbach
Marmot (species not given)	Simon	+	?	+	+	?	?	4 specimens examined
Marmota monax (Arctomys monax, American marmot, ground hog, woodchuck)	Bonnot	+	+	?	?	?	?	Complete ramification not given

SPECIES	AUTHOR	+ = PRESENT, – = ABSENT						REMARKS
		Cervical	Scapular	Axillary	Thoracic	Renal	Inguinal	
Marmota monax rufescens	Cushing and Goetsch	?	?	?	+	?	?	3 specimens examined
Marmota monax rufescens	Rasmussen	+	+	+	+	–	–	120 specimens examined
Cricetus cricetus (Cricetus frumentarius, European hamster)	Sulzer	+	+	+	?	–	–	
Cricetus cricetus (Cricetus frumentarius, European hamster)	Friedleben	?	?	?	?	?	?	Cited by Auerbach
Cricetus cricetus (Cricetus frumentarius, European hamster)	Auerbach	+	+	+	+	+	–	Only 1 specimen examined
Castor fiber (beaver)	Tiedemann	?			?			Described as enlarged thymus
Couia (?) (a genus allied to beaver)	Simon	+	?	+	+	?	?	Developed as well as in the marmot
Citellus citellus (Spermophilus citellus, ground squirrel)	Horvath	+	+	+	+	?	?	
Citellus citellus (Spermophilus citellus, ground squirrel)	Pallas	+	?	+	?	?	?	Cited by Auerbach
Citellus citellus (Spermophilus citellus, ground squirrel) (?)	Vignes	?	?	?	?	?	?	Distribution not given
Citellus tridecemlineatus (13-lined ground squirrel)	Mann	+	?	?	+	?	?	Only incidentally mentioned
Microtus arvalis (Hypudaeus arvalis)	Pallas	?	?	?	?	?	?	Presence merely mentioned
Lemmus lemmus (Myodes lemmus, Mus lemmus, lemming)	Pallas	+	–	–	–	–	–	Cited by Auerbach
Microtus lagurus (Mus lagurus)	Pallas	–	–	+	–	–	–	Absence in thoracic region seems especially questionable

Cricetulus arenarius (Mus arenarius)	Pallas	+	−	+	−	−	−	
Phodopus songarus (Mus songarus)	Pallas	+	−	+	−	−	−	
Alactaga saliens (Mus iaculus)	Pallas	+	−	−	−	−	+	
Sicista subtilis (Mus vagus)	Pallas	+	−	+	−	−	−	
Rattus caraco (Mus caraco)	Pallas	+	−	−	−	−	−	
Rattus norvegicus (Mus decumanus, brown Norway rat)	Sulzer	+	+	+	?	?	?	
Rattus norvegicus (Mus decumanus, brown Norway rat)	Jacobson	?	?	?	+	?	?	Distribution not given
Rattus norvegicus (Mus decumanus, brown Norway rat)	Hammar	+	+	+	+	+	+	Black-white variety used
Rattus norvegicus (Mus decumanus, brown Norway rat)	von Hansemann	+	+	+	+	+	−	
Rattus norvegicus (Mus decumanus, brown Norway rat)	Auerbach	+	+	+	+	+	+	13 specimens examined
Rattus norvegicus albinus (white rat)	Vignes	?	?	?	?	?	?	Distribution not given
Rattus norvegicus albinus (white rat)	Cramer	+	+	+	+	+	?	Surrounds ovary in female
Rattus norvegicus albinus (white rat)	Rasmussen	+	+	+	+	+	+	6 specimens examined
Rattus rattus (Mus rattus, black rat)	Auerbach	+	+	+	+	+	+	4 specimens, 2 being young
Rat (species not given)	Mietens	?	?	?	+	?	?	Noted polylocular fat in inguinal region
Rat (species not given)	Bonnot	+	+	?	?	?	?	Complete ramification not given
Mus musculus (common house mouse)	Afanassiew	+	+	+	+	?	?	In locations given by Barkow

SPECIES	AUTHOR	+ = PRESENT, — = ABSENT						REMARKS
		Cervical	Scapular	Axillary	Thoracic	Renal	Inguinal	
Mus musculus (common house mouse)	Jacobson	?	?	?	+	?	?	Complete ramification not given
Mus musculus (common house mouse) (?)	Ehrmann	?	?	?	?	?	?	Presence merely mentioned
Mus musculus (common house mouse)	Auerbach	+	+	+	+	+	+	3 specimens examined
Mus musculus (common house mouse) (?)	von Hansemann	?	+	?	?	?	?	Best developed in interscapular region
Mus musculus (common house mouse) (?)	Vignes	?	?	?	?	?	?	Distribution not given
Mus musculus (white mouse)	Mietens	?	?	?	+	?	?	Noted polylocular fat in inguinal region
Mus musculus (tame mouse)	Cramer	+	+	+	+	+	?	Surrounds ovary in female
Microtus agrestis (Arvicola agrestis, field mouse)	Auerbach	+	+	+	+	+	+	3 specimens examined
Field mouse (species not given)	Vignes	?	?	?	?	?	?	Distribution not given
Muscardinus avellanarius (Myoxus muscardinus, dormouse)	Auerbach	+	+	+	+	+	+	2 specimens examined
Muscardinus avellanarius (Myoxus muscardinus, dormouse)	Polimanti	+	+	+	+	+	+	5 specimens examined
Eliomys quercinus (Myoxus nitela, dormouse)	Prunelle	?	?	?	+	?	?	Complete ramification not given
Eliomys quercinus (Myoxus nitela, dormouse) (?)	Meckel	+	?	+	+	?	?	

Eliomys quercinus (Myoxus nitela, dormouse) (?)	Wagner	+	?	+	+	?	?	
Eliomys quercinus (Myoxus nitela, dormouse (?)	von Hansemann	?	+	?	?	?	?	Interscapular best developed
Eliomys quercinus (Myoxus nitela, dormouse)	Auerbach	+	+	+	+	+	+	6 specimens, at least, examined
Glis glis (Myoxus glis, fat dormouse)	Polimanti	+	+	+	+	+	+	5 specimens examined
Sciurus vulgaris (old world squirrel)	Hirzel and Frey	–	–	–	+	–	–	
Sciurus vulgaris (old world squirrel)	Auerbach	–	–	–	+	–	–	2 specimens examined
Sciurus vulgaris (old world squirrel) (?)	Vignes	?	?	?	?	?	?	Well developed, location not given
Sciurus carolinensis (N. Amer. grey squirrel)	Bonnot	+	+	?	?	?	?	Complete ramification not given
Glaucomys volans (Sciurus volans)	Pallas	?	?	+	?	?	?	Cited by Auerbach
Oryctolagus cuniculus (Lepus cuniculus, common European rabbit)	Ehrmann	?	+	?	?	?	?	Varied from brown to ordinary white adipose tissue
Oryctolagus cuniculus (Lepus cuniculus, common European rabbit)	Auerbach	–	–	–	–	–	–	3 specimens examined
Oryctolagus cuniculus (Lepus cuniculus, common European rabbit)	von Hansemann	?	+	?	?	?	?	Best developed in scapular region
Rabbit (species not given)	Bonnot	+	+	?	?	?	?	
Rabbit (species not given)	Cramer	?	?	?	?	+	?	Complete distribution not given
Rabbit (species not given)	Bensley	+						Brown fat probably similar in origin to hib. gld.
Lepus timidus (common European hare)	Auerbach	+	+	+	+	+	+	Small in all places

SPECIES	AUTHOR	+ = PRESENT, − = ABSENT						REMARKS
		Cervical	Scapular	Axillary	Thoracic	Renal	Inguinal	
Ochotona alpinus (Lepus alpinus)	Pallas	?	?	?	?	?	?	Presence merely mentioned
Cavia porcellus (Cavia cobaya, guinea pig)	Meckel	?	?	?	?	?	±	Not constant
Cavia porcellus (Cavia cobaya, guinea pig)	Auerbach	−	−	±	±	±	−	6 specimens, small when present
Cavia porcellus (Cavia cobaya, guinea pig)	von Hansemann	?	+	?	?	?	?	Best developed in scapular region
Cavia porcellus (Cavia cobaya, guinea pig)	Polimanti	−	±	±	±	−	−	8 specimens, small when present
Cavia porcellus (Cavia cobaya, guinea pig)	Vignes	?	?	?	?	?	?	Well developed in certain cases. Location not given
Cavia porcellus (Cavia cobaya, guinea pig)	Cramer	+	?	?	?	+	?	Complete ramification not given
Carnivora								
"Wiesel" (European weasel, probably Mustela putorius)	Auerbach	?	?	?	?	?	?	Not certain but probably present
"Marder" (European marten, probably Martes martes)	Auerbach	?	?	?	?	?	?	Not certain but probably present
Meles meles (Meles taxus, European badger)	Jacobson	−	−	−	−	−	−	This is a hibernating species without any hibernating gland
Meles meles (Meles taxus, European badger)	Friedleben	−	−	−	−	−	−	
Meles meles (Meles taxus, European badger)	Auerbach	−	−	−	−	−	−	

Procyon lotor (raccoon)	Cushing and Goetsch	–	–	–	–	–	–	Three specimens, hibernating species
Felis domestica (cat)	Hammar	–	–	–	–	–	–	
Felis domestica (cat)	Auerbach	–	–	–	–	–	–	
Felis domestica (cat)	Bonnot	+	+					Refers to dorso-cervical fat mass and included lymph glands
Felis domestica (cat)	Polimanti	–	–	–	–	–	–	3 specimens examined
Canis familiaris (dog)	Bonnot	+	+					Refers to dorso-cervical fat mass and included lymph glands
				Ungulata				
Sus scrofa (common pig)	Bonnot	+	+					Refers to dorso-cervical fat mass and included lymph glands
				Homo (man)				
Two 50 mm. embryos, 9 yr. child, 28 yr. woman	Auerbach	–	–	–	–	–	–	
75–260 mm. embryos	Hatai	+	+					"Interscapular gland," probably corresponding to hib. gland
20 adults, 12 embryos	Bonnot	+	+					Refers to dorso-cervical fat mass and included lymph glands
5 mo. foetus and several cretins	Shattock	+	+	+				Refers to fat masses in same position as hibernating gland in hedgehog
41 embryos, 1 newborn, 32 adults	Berg	–	–	–	–	–	–	Interscapular fat no different from fat elsewhere
	Cramer	?	?	?	?	+	?	Only perirenal tissue mentioned

is different histologically, physiologically and embryologically from the true hibernating gland. But certainly, as far as the albino variety is concerned, there is no evident histological differences between the brown fat found along the large vessels of the lower abdominal and pelvic region and that in the other typical positions such as the axillary, as is plainly evident by comparing figure 17, which is taken from the region of the common iliac vessels, and figure 18, which is from the typical axillary lobe of the hibernating gland of the same large fat adult white rat. This was true of all six adult animals taken at random from the colony at the Institute of Anatomy, University of Minnesota. The brown multilocular fatty tissue in this so-called inguinal region is, however, in smaller masses and less evident because of greater admixture with ordinary adipose tissue. In the white rat, as well as in many other animals, as shown in figure 19, which is a low power photograph of the interscapular lobe, there is more or less ordinary adipose tissue in the capsule and between the lobules even in those regions (thoracic, cervical, and axillary) where the hibernating gland is most fully developed.

IS THERE ANYTHING IN THE HUMAN BODY THAT IS HOMOLOGOUS TO THE HIBERNATING GLAND OF ANIMALS?

Rather definitely circumscribed masses of adipose tissue, particularly in the interscapular and dorso-cervical region, in man have been described by various anatomists. F. Merkel ('99) in his Topographische Anatomie considers them under the head of 'Fettpolster.' He compared them to the sucking pad (corpus adiposum buccae—a sharply outlined mass of adipose tissue in the cheek, partly between the masseter and buccinator muscles and partly covered externally by superficial facia and zygomatic muscle). As pointed out later by Shattock ('09) and Scammon ('19), the sucking pad contains only unilocular fat cells of the ordinary type, while these dorso-cervical fat masses are apparently characterized, at least for a considerable time, by multilocular fat cells. Charpy ('01) speaks of these structures in the human subject as 'coussinet adipeux.' A similar mass described by him in 1907 under the superficial fascia in the lateral lumbar and gluteal region, extending from the level of the twelfth rib to as low as the major trochanter, need not be considered in this connection since it is less constant and far away from any situation where the hibernating gland tissue has been found. It was Hatai ('02), however, who first called particular attention to the apparent homology between these dorsal and cervical fat masses and the hibernating gland. He described them in five human embryos, varying in length from 75 mm. to 260 mm. He termed this fat tissue 'interscapular gland' and from its position and character considered it as probably corresponding to the hibernating gland of lower mammals. A more extensive examination of these fat masses in the human subject was reported by Bonnot ('08), who investigated a series of twenty adults and twelve embryos from 32 mm. to 280 mm. in length (uterine position). This latter author concluded that they vary in volume with the condition of the individual, being most pronounced in the well nourished, in which case the gland cells proper contain fat. He further considers it probable that the structure is present in all mammals, that in man it is homologous to the hibernating gland of rodents.

Shattock ('09) came to a similar conclusion. He claims to have independently observed in the human subject this fat mass, which Hatai called interscapular gland, before being aware of Hatai's publication. In a human foetus of five months he found this deep seated fat of the neck near the carotid artery presenting the character of the hibernating gland, the parenchymal cells being nearly all multilocular and containing a distinct cytoplasmic framework about the fat droplets. The fat globules usually varied in size. The histological picture was essentially like that of the hibernating gland of the hedgehog. The fat cells of the surrounding ordinary subcutaneous tissue of the same individual were, as usual, unilocular. Furthermore, the multilocular fat tissue of the interscapular gland was arranged in lobules separated by septa of connective tissue. Frequently lymph nodes (deep cervical glands) were embedded. In a cretinous female at full term he found similarly this polylocular fat in the posterior triangle of the neck beneath the sterno-mastoid muscle and on the outer side of the great vessels. Another mass was located in the axilla beneath the pectoralis minor and extending beyond both upper and lower margins of this muscle. He presents a drawing of a cross-section of the neck of another cretinous foetus showing that these fat masses occupy the same position as does the hibernating gland of the hedgehog. He also states that the volume of these masses varies with the condition of the individual, being most prominent in well-nourished subjects. In a patient being treated with thyroid extract he noted that the prominent axillary and cervical fat masses disappeared. He concludes, "What I venture, then, to suggest in regard to these fatty swellings in the neck of such cretins is that they are not mere fortuitous local accumulations of fat, but that they are enlargements of the structures found in the neck of the hedgehog" (p. 257).

The prominence and fatty character of these masses in connection with thyroid disorders was described as early as 1850 by T. B. Curling and again by H. Fagge in 1871.

Cramer ('20) stresses the glandular character of the perirenal fat, which he says has in all embryos a characteristic gland-like structure, which is retained in some adult animals (mostly hibernating) but in most animals (including man) it acquires the appearance of ordinary adipose tissue soon after birth. According to Hammar ('95) and others, the perirenal adipose tissue arises from so-called primitive fat organs in contradistinction to the origin of subcutaneous fat which develops in ordinary connective tissue cells.

There is, on the other hand, some negative evidence. Berg ('10) in an investigation of the development of the fatty tissues based upon a study of forty-one human embryos from 40 mm. and up, one newborn, thirty-two adults and some animals (young rabbits, guinea pigs and mice), included under the head of 'Intermuskuläres Fett' the fatty bodies of the cervical region mentioned by Merkel, Charpy and Shattock and termed 'interscapular gland' by Hatai and Bonnot. He found, however, no evidence of any special development in these cervical masses to distinguish them from other adipose tissue. He says, "Es konnte kein Anhalt dafür gefunden werden, dass das Gewebe des Halsfettkörpers eine besondere Stellung dem andern Fettgewebe gegenüber einnimmt, wie dies Bonnot zu zeigen suchte" (p. 340). Auerbach ('02) indicates in his table (p. 328) that he could find nothing in two 50-mm. human embryos which he could identify as hibernating gland. Shattock ('09) admits that like the thymus the multilocular fat, even if a distinct and glandular structure different from ordinary adipose tissue, might be partly or entirely replaced in time by ordinary adipose tissue. This might account for Auerbach's inability to find the 'interscapular gland' in a nine-year-old child and only a few multilocular cells in a woman 28 years old. More or less on the negative side is also H. Batty Shaw ('02), who studied human foetuses from the fourth month to maturity as well as infants and older subjects of all ages and concluded that there were no polygonal highly protoplasmic cells acting as precursors of fat formation. Yet he goes on to describe in sections of subpleural and axillary adipose tissue large cells with abundant granular cytoplasm having but little and frequently no fat. These cells are usually closely packed and therefore polygonal in form. He found them present in human foetuses near term. Two or three weeks after birth, he found that in the subpleural adipose tissue unilocular fat cells were the exception and multilocular were less frequent than earlier; but the large polygonal cells, relatively free from fat and with a very rich capillary plexus, were found in every field of the microscope either singly or in irregular groups interspersed with groups of cells possessing usually several fat globules. In older infants he found an abundance of uni- and multilocular fat cells and only here and there one of these polygonal fat-free cells. Subjects six years and older contain, according to this author, only the ordinary unilocular fat cells. The above description, he says applies as well to the axillary adipose tissue.

While we cannot go into the discussion of adipose tissue development, the above statements and others to follow are meaningless without having in mind the two much discussed theories usually associated with the names of Flemming and Toldt.

The former especially championed the view that adipose tissue is merely a loose fibrous connective tissue in which the ordinary branched connective tissue cells have become filled with fat; i.e., adipose tissue is not a separate distinct tissue. This was called secondary adipose tissue formation by Hammar. The other theory, advanced by Toldt and others, assumes that adipose tissue is a specific tissue which develops from definitely organized groups of mesenchymal cells that are round or polygonal before fat is deposited. This constituted Hammar's primary adipose tissue formation. This special pre-adipose structure was called 'Fettkeimlager' by Toldt and 'Primitivorgane der Fettläppchen' by Kölliker. Like Hammar, some have supposed that adipose tissue may arise by both methods. Probably Bell ('09), who made a special study of the histogenesis of adipose tissue and to whom the reader is referred for an unusually good review of the essential literature, gives as concise a statement on this point as is to be found. He says:

> The preadipose tissue varies in different regions in the quantity developed before the true fat cells begin to form, and it remains in the preadipose condition longer in some situations than in others; but the differences are not marked enough to warrant Hammar's classification (into primary and secondary adipose tissue formation). The term, primitive fat organ, may however be retained, if desired, to designate the renal preadipose tissue, since this tissue is more sharply marked off than preadipose tissue in other situations and persists longer in the preadipose condition (p. 416).

To summarize, it may be said that there is no direct or very convincing evidence in the literature (and especially in the illustrations published) that either the dorso-cervical or axillary perirenal masses of adipose tissue in man are homologous to the brown adipose tissue or hibernating gland of animals, although it may develop from so-called primitive fat organs. The discussion about the presence of absence of multilocular fat cells proves nothing because it is not clear, as a rule, what these cells looked like and may, therefore, be nothing but earlier stages in ordinary adipose tissue development. A hasty examination of the perirenal fat of a half dozen human specimens from birth to two years of age that happened to be at hand showed that in two cases, one newborn and one about one and one-half years old, contained a variable amount of cells essentially like those found in the hibernating gland of animals. A low power photograph of parts of two masses of such cells is shown in figure 15 and a high power retouched photograph to show general cellular characteristics is shown in figure 16. These illustrations are from the newborn. A comparison of figure 16 with figures 17 and 18 (on the same plate) show the striking similarity between the multilocular adipose cells and the typical hibernating gland cells of the rat, for example. There is needed, however, an extensive and thorough examination of human material to say how frequently and to what extent this multilocular type of adipose tissue occurs. It is to all appearances quite different from developmental stages of ordinary adipose tissue which is finally characterized by unilocular cells.

DEVELOPMENT OF THE HIBERNATING GLAND

The literature on the development of the hibernating gland is very meagre. While Ecker ('53) remarks that in young animals it is relatively richer in proteins and poorer in fat droplets, Afanassiew ('77) seems to have been about the first to study its development. The latter author states that in hedgehogs, even in the mediastinal region, it develops from indifferent cells; that it is gray and juicy in young animals and becomes brown and more fibrous with age. He also gives the size of the cells at different ages as compared with thymic cells. Ehrmann ('83) and Carlier ('93), also from a study of the hedgehog, decided that the cells arise in much the same way as ordinary adipose cells (except for the formation of more cytoplasm and the failure of the globules to unite into a single droplet) from round uninucleated granular connective tissue cells. Ehrmann, therefore, considers it merely as the adipose organ common to mammals in general.

The most thorough studies of the embryology so far discovered are those by Hammar ('95) and von Hansemann ('02). Hammar investigated rats from 6 mm. to 15 cm. in length and found that an anlage in the interscapular region was first differentiated in foetuses 1.2 in length. The connective tissue cells arrange themselves in lobes in relation to particular blood vessels. While originally branched, these cells increase in volume so that they become closely packed and polygonal in form before any fat appears within them. The fat, as a few small droplets, first appears during the latter part of intrauterine life. Within a day or two after birth the cells increase rapidly in size due to the accumulation of fat-droplets which may fuse with each other till in some cases there results a droplet sufficiently large to crowd the nucleus to one side. Such a cell is, however, much richer in protoplasm than the ordinary adipose tissue cell. He argues that the fatty body in the dorso-cervical region of such animals as the rabbit, cat, guinea pig, etc., develops essentially in the same manner, except that the cells become more gorged with fat, and hence these structures should be regarded as homologous. Von Hansemann, working on the rat, mouse and hedgehog agrees in most particulars with Hammar. In the rat he noted the first appearance in the cervical and axillary region in foetuses 1.6 cm. long and a little later in the neighborhood of the thymus. Relatively large blood vessels appear before the cells are differentiated in the case of the rat. In man and some other animals homologous vessels could not be identified. He also describes characteristic veins, grouped in two trunks, which bend around the vertebral column, uniting just ventral to it and emptying directly into the superior vena cava. He believes that the differentiation of the cells of connective tissue origin of this region, resulting in the formation of the hibernating gland, depends upon the existence of these vessels because the organ is found only in those animals in which these vessels are especially well developed. It is evident, he says, that there are embryological differences between the hibernating gland and ordinary adipose tissue. These differences are based upon the place of development as well as the histogenesis. One type does not change into the other. In regard to Hammar's classification of fatty tissues, he states that it is evidently based upon a new departure from the accepted definition of adipose tissue as developed by Toldt.

He discusses the relation of the marked lordosis found in hibernating animals to the hibernating gland, maintaining that this spinal curvature in the upper thoracic region develops simultaneously with the growth of the dorsal lobes of the gland. This lordosis appears long before birth—beginning in rats at the 16-mm. stage. The similar but less marked curvature in the region of the dorsal fat body of non-hibernating species (guinea pig, rabbit, etc.) appears later under the influence of the enlargement of the dorsal fat mass and the assumption of locomotion.

Auerbach ('02) however, thought he observed in rats, dormice and marmots a distinct transformation of this brown fatty tissue into ordinary white adipose tissue—the development of the fat being related to the prominent cytoplasmic granules. Mietens ('08), who in connection with a study of the thymus mostly in rats and white mice reports evidences in support of another possibility, noted what appeared to be transformation of reticular cells of the involuting thymus to hibernating gland cells. Simon ('45) many years before this came to a similar conclusion for he said: "in all cases where the thymus becomes a permanent organ, it does so under an altered character, namely, by a singular and striking transformation of its ultimate elements—by developing its natural cytoblasts and fluid contents into a system of nucleated fat cells, held within a limitary membrane."

Stannius ('53) had the idea that the sympathetic nervous system of the marmot developed from its interior.

The histogenesis of the so-called interscapular gland of human embryos was traced by Bonnot ('08) with the conclusion that it is derived from the walls of the primitive internal jugular vein. First there appears unique lobules from which are differentiated lymphoid tissue and the fat containing tissue. The lymphoid tissue finally differentiate into lymph nodes and hemolymph nodes.

According to Long ('22) the interscapular lobes are first visible in the seventeen day embryo rat. At term these lobes together with their cervical extensions constitute a mass nearly as large as the liver.

FUNCTIONAL SIGNIFICANCE

A structure that evidently was the hibernating gland of the mediastinal region of the marmot was first mentioned by Velsch in 1670. He thought it was of a lymphatic nature and functionally related to the thymus. A few years later, Harder (1686) stated that it evidently had some specific function since it produces a fatty secretion. A number of subsequent writers (Pallas, 1778; Meckel, 1806 and 1815; Mangili, 1807; Prunelle, 1811; and Tiedemann, 1815) considered it a part of the thymus. Since Meckel (1806) also found a persistent thymus in seals and dolphins, he concluded that this structure does not undergo the usual involution in animals that live under ground or in the water and is therefore functionally related to the lungs. Later (1815) he suggested that the enlargement of the organ during hibernation acts mechanically on the lungs and great vessels so as to retard greatly and in other ways change respiration and circulation. This, of course, does not follow because circulation and respiration go on at the usual rate in the autumn for a long time before dormancy sets in and during the existence of a maximum hibernating gland.

It was Ludwig Jacobson (1817) who first clearly distinguished it from the thymus. As a result of a study of the marmot, hedgehog and bat, he concluded that Pallas, Meckel, Prunelle, and Tiedemann were wrong in their descriptions of the growth of the thymus during certain seasons of the year and pointed out that the structure which thus shows marked seasonal change is an entirely separate organ. He found that the thymus proper is separated from this fatty organ by its own membrane, that there is a great difference in the cellular structure between them and that the thymus in these animals undergoes the usual atrophy. To him the hibernating gland was merely a modified form of adipose tissue. This was fully corroborated by Haugstedt in 1831.

Rudolphi ('30) and Wagner ('35) similarly considered it only as a modified form of adipose tissue serving as reserved food; but Burdach ('30), Simon ('45) and Jones ('52) adhered to the old notion that it is a persistent thymus, although Simon and

Jones recognized that it may become transformed into a mass of fat cells. Simon thus recognized two secretions produced by the thymus—one of a fluid character and only temporary and another of solid fat which is a permanent secretion characteristic of hibernating animals and related to respiration, muscular motion, etc.

Barkow ('46), who was the first to call it the hibernating gland ('Winterschlafdrüse'), although recognizing that it was a separate organ from the thymus, considered that it belonged with the ductless glands. Ecker ('53), Valentine ('57, '59), Leydig ('57), Friedleben ('58), Vogt and Yung ('94) and Wiedersheim (at least as late as 1907) regarded it as a member of the hemopoietic organs.

A further blow to the idea that there was some similarity, in structure at least, between the hibernating gland and the blood-forming organs was struck by Hirsel and Frey ('63), who investigated histologically this structure in six different species and could see no similarity between these sets of structures, although their description of the fat droplets being found in the interstices of an intercellular network of fine fibrils has never been supported. That it is merely a variety of adipose tissue, serving as a source of food material during winter-sleep, has been the predominating opinion since this time; this being also the idea of Owen ('68), Fleischel ('69), Afanassiew ('77), Ehrmann ('83), Poljakoff ('88), Carlier ('93), Hammar ('95), Dubois ('96), von Hansemann ('02), Auerbach ('02), Bonnot ('08), and Polimanti ('12). Afanassiew believed also that its characteristic brown color depends upon pigment granules in the stroma and that this pigment contains hemoglobin which furnishes oxygen for the oxidation of fat during hibernation. That it serves in addition as packing material for the protection of important organs was suggested by Poljakoff ('88) and Polimanti ('12). Polimanti considered that the protection was mainly against the low external temperature in winter. Its presence in non-hibernating forms (which was noted as early as 1774 by Sulzer) is explained by Polimanti on the grounds that it is an atavism, dating back to a remote period when their ancestors hibernated. Since Bonnot considers the associated lymph nodes as a part of the gland, he thinks it can under certain conditions function also as a scavenger for red corpuscles and as a blood-forming organ.

While the hemopoietic nature of the hibernating gland is unsupported by morphological or other evidences and has therefore been discarded, the theory that it is an endocrine organ of some sort persists. Thus Malesani ('02) was struck with its glandular appearance and thought it must be of great importance in keeping up nutrition during winter sleep. Shattock ('09), because of the discrete droplets of lipoid which its cells contain, thinks it is allied to the ductless gland and serves some special function since it is largely spared during the major portion of dormancy. Salmon ('10, '16) argues that it is the only organ that is very active during winter sleep and therefore functions as a true endocrine organ by inhibiting all other glands of internal secretion.

All these ideas are, of course, mere speculations. Very little experimental work of any kind has been carried out. Apparently the first extirpation experiments on record in connection with this multilocular fat tissue are those by Dubois ('96). He first merely exposed the structure in the marmot to see the effects of the necessary preliminary operative procedure. On the following day as much of the tissue as possible was removed. Two of the animals lived two or three days and during this time they exhibited no difficulty in warming up rapidly after torpor. But only a portion of the tissue can be removed. Auerbach ('02) extirpated the dorsal part of the hibernating gland in a rat. The animal lived two months. There was no regeneration of the lost tissue, its place being occupied by ordinary adipose tissue.

As the results of an extensive series of extirpation experiments in connection with the utilization of extracts of the hibernating gland on white rats and mice, Vignes ('13) found that while most of the rats survived the removal of a large part of the organ (it is improbable that complete removal could be done) they lost weight and finally died. Only two lived more than three months. One lived four and one-half months. In the mouse, where the operation is more difficult, the animals survived indefinitely, although there was an initial loss of weight. The operated rats had an increased resistance to adrenalin and cobra venom and a lessened resistance to chloroform. He also found that the extract of this fatty tissue increased the toxic power of tetanus toxin. The organ also apparently modified enzyme action for its extirpation diminished the quantity of lipase in the serum of the rats. It contained a lipase which acted on monobutyrin. The amyloptic power of the serum of operated rats was diminished; but extracts of the organ did not act on starch. The extract had an antitryptic power since it inhibited the action of trypsin. Vignes suggests that further studies on this organ would increase our understanding of the rôle of the phosphatides in metabolism. He concluded that the organ may be considered as an economizer of proteins by insuring first the utilization of reserved carbohydrates and fats.

Finally Cramer ('20), after working mostly with white rats and tame mice, but also with the perinephric fat of the guinea pig, rabbit and man, concluded that in all these types of mammals there exists a glandular type of adipose tissue histogenetically and functionally distinct from ordinary adipose tissue. He lays stress upon the fact that the fatty material of this special glandular adipose tissue is rich in cholesterin compounds and other lipoids, in addition to true fat, and that these lipoids are retained during emaciation, but used up in animals dying from having been on a vitamine-free diet. With the loss of lipoid, it comes to resemble a very vascular endocrine organ. Possibly, he thinks, the lipoid has been used up to supply vitamine. Vitamine deficiency also causes great loss of lipoid from the suprarenal cortex. From the great similarity in the reaction to polarized light between the adrenal cortex and the adjacent glandular adipose tissue, he assumes that there is also great similarity in composition. Afanassiew ('77) also tried to show a similarity in function between the suprarenal and the pigment in the hibernating gland. Cramer thinks the 'glandular fat' is also closely related in function to the thyroid gland and calls attention to adipose accumulation in cretins, as has already been mentioned. He, therefore, concludes that disturbance of the functional activity of this glandular adipose tissue will have to be taken into consideration in connection with deficiency disease. It would seem, however, that the facts upon which so much importance is based are rather meager. His evidence is too indirect to be taken as proof that the ductless glands are closely related to this special adipose tissue.

The history of the hibernating gland from a functional point of view may thus be divided into three or four periods. First there is a long interval (1670 to 1817) during which it was generally mistaken as a part of the thymus. Then followed a period (1817 to 1863) in which it was recognized as a separate organ from the thymus but still a ductless gland usually of the hemopoietic series. Quite generally since about 1863 and by several writers even before this, it has been looked upon as a modified form of adipose tissue serving merely as reserved food. Finally its endocrine character has been revived several times especially since 1902. It is clear, however, that there is no evidence pointing at all strongly to its internal secretory character. As a matter of fact no research has yet gone extensively enough into its phylogeny and its physiological significance to give data of any reliance. So it would seem unwise at present to take very seriously the suggestion that this brown polylocular adipose tissue should be grouped with the endocrine organs.

THE HIBERNATING GLAND OF THE WOODCHUCK (MARMOTA MONAX RUFESCENS)

While the hibernating gland of the American marmot, or woodchuck, has been mentioned by a few writers, this has been only incidentally, so that no detailed description of this structure in this most favorable species has been found. Since this animal is a profoundly hibernating form found in abundance over a wide area of the United States (Howell, '15), it may at any time come into use in experimental and other investigations where the organ under consideration may be involved. The time is therefore opportune for a careful statement of its extent and structure.

Position and relation of the various lobes in the adult animals before hibernation

The intrathoracic portion, as shown in figure 1, may be divided into four lobes. The largest one occupies the superior mediastinum. It is molded on the superior surface of the pericardium and about the great vessels, trachea, and lateral sides of the oesophagus, as shown in figure 6. Where it comes in contact with the pericardium several blunt appendages of ordinary adipose tissue are attached to the margin of its lower border. In its interior is the atrophied thymus (fig. 6) which consists of two ventrally situated lobes, so small as to constitute a very insignificant part of the entire mass. The thin upper apex of the lung forms the lateral and ventral boundary of its caudal two-thirds. The two upper ribs and intercostal space form the lateral boundary of cephalic third, while the ventral surface of this portion is in contact with the sternothyroid muscles.

From the dorsal portion of the above central mass, a long caudally directed lobe, nearly surrounding the descending aorta, extends to the diaphragm in the posterior mediastinum; but there are no extensions into the abdominal cavity. This lobe may roughly be divided into three parallel subdivisions. One of these, the ventromedial, is the smallest. It runs along the ventral wall of the aorta to the point where the aorta pierces the diaphragm, where a little ordinary adipose tissue takes its place and follows down into the abdomen. The other two, right and left lateral portions, are found under the parietal pleura dorsal and lateral to the aorta, each surrounding the sympathetic trunk and giving off short intercostal spurs in most of the intercostal spaces. These two dorsolateral masses meet along the median line in front of the bodies of the vertebrae and posterior to the aorta. Caudally at about the tenth or eleventh rib each is split by the psoas major muscle. The lateral prong extends only a short distance when it is replaced by ordinary adipose tissue which follows a variable distance along the lateral border of the muscle. The other prong runs in the angle between the aorta and psoas major as far as the diaphragm where it is similarly replaced by ordinary fat which continues into the abdominal cavity.

From each ventrolateral surface of the upper portion of the superior mediastinal lobe there is an extension along the internal mammary vessels as far as the sixth costal cartilage. These lobes are for the most part wedged in between the costal cartilages, intercostal muscles and the transverse thoracic muscle. In figure 1 the transverse thoracic muscle has been reflected backward to expose the hibernating gland and internal mammary vessels. It is seen that at each costal cartilage there are two lateral spurs from the main lobe—one just above and one just below the cartilage. These lateral projections may be as long as two centimeters. Connecting the isolated masses and extending beyond both the main lobe along the internal mammary vessels and the side spurs is considerable ordinary adipose tissue, which has not been included in the drawing in figure 1 since it would greatly detract from a clear presentation of the extent of hibernating gland tissue.

From careful dissections it was found that the intrathoracic portion constitutes about one-third of the combined weight of all the hibernating gland tissue and weighs in the neighborhood of 20 grams in an animal with a net body weight of 3000 grams.

The cervical portion of the hibernating gland in part consists of two lobes extending upward from the superior mediastinal mass. Figure 1 shows the left lobe which at first is under the sternothyroid muscle but shifting laterally till it comes to lie under the sternomastoid muscle. These lobes follow the carotid arteries, most of the gland being ventral to the vessels and against the lateral wall of the trachea. A short distance above the clavicle these lobes break up into numerous smaller masses which follow along the sides of the trachea and oesophagus and along the internal jugular veins and carotid arteries through the entire cervical region, as shown in figure 2. Thin ribbons may partly encircle the ventral and lateral walls of the trachea in the grooves between the tracheal rings. Larger masses are found in the angle between the trachea and oesophagus, the upper ones coming in contact with the thyroid gland. Smaller ones may be found wedged in dorsal to the oesophagus. The cervical lymph nodes are usually surrounded by hibernating gland tissue. Scattered masses also spread out laterally under the cleidomastoid and omohyoid muscles to become continuous with a much larger lobe in the posterior triangle of the neck, as illustrated in figure 2.

One of the two largest lobes in the cervical region is illustrated in figure 3. It lies under and dorsal to the major levator scapulae muscle and superiorly it also extends over the superficial (lateral) surface of that muscle. The central portion is split by the deep rhomboideus muscle; but at the base of the skull and again in the caudal region of the neck it is continuous over the lateral surface of this muscle. Its deep surface rests on the scalenus muscle and its superficial surface is largely covered by the trapezius. Just above the scapula it enlarges greatly and spreads out on the superior, and to some extent also on the lateral, surface of the supraspinatus muscle. Branches of the transverse scapular vessels are seen passing along the lateral surface of the caudal portion of this lobe and to continue beyond the gland accompanied by some ordinary adipose tissue.

From the dorsal edge of this lobe there is a backward extension along the upper surface of the supraspinatus muscle and under the occipitoscapular muscle. This lobe is indicated by a broken line in figure 3. This portion of the gland extends to the vertebral border of the scapula. It does not strictly speaking become interscapular in the woodchuck but undoubtedly would be so designated by some. There is no superficial lobe strictly in the interscapular region such as is found in the white rat and many other animals.

Two smaller detached lobes are found in the extreme dorsal portion of the neck, deeply situated one on the under surface of each semispinalis capitis muscle near the median line. The location is shown in figure 4, which is from a young animal between two and three months old. These lobes, even in the adult, reach only slightly into the interscapular region. In the adult each lobe is about three centimeters long and about one-third as wide and about one-tenth as thick. Branches of the third, fourth and fifth cervical nerves cross the deep surface of the gland. Figure 4 was taken from a young animal to illustrate how each lobe appears during development as a series of small round nodules usually along the course of some blood vessel (the deep cervical in this case). These nodules have an entirely different appearance from developing ordinary adipose tissue.

The various cervical lobes taken together constitute about one-fourth of the entire gland.

Nearly one-half of the gland is found in the axillae. A typical axillary lobe, as shown in figure 5, is triangular in cross-section. It rests on the chest wall covering the scalenus muscle. The ventral surface is moulded by the pectoral muscles and the lateral surface is shaped by the latissimus dorsi, teres major and subscapular muscles. It follows the lateral thoracic vessels as far as the fourth rib where its tapering caudal extremity is replaced by ordinary adipose tissue which may continue a considerable distance farther along the vessels. In it are embedded the axillary lymph nodes. Its upper portion surrounds the large axillary vessels and nerves. A narrow extension ascends along the ventral surface of the scalenus muscle and under the clavicle to become continuous with the large cervical lobe in the posterior triangle of the neck.

The two axillary lobes together constitute nearly 1 per cent of the reduced (net) body weight and all the rest of the organ makes up fully another per cent, the total gland representing about two per cent of the body weight.

Microscopic structure

All the lobes are identical in histological appearance. As shown in figure 6, the lobulation seen on the surface with the unaided eye is also characteristic throughout the entire mass. Only a small amount of connective tissue separates the lobules from each other and the connective tissue within a lobule is almost negligible. But there is an unusually rich plexus of capillaries around each fat-containing cell. This is illustrated well in figure 11, which is from a specimen prepared by injecting the fixer into the arteries after the blood had been washed out. While this abundant blood supply has attracted the attention of many, the fact has rarely been adequately illustrated. The great bulk of the organ, therefore, consists of epithelial-like cells which vary greatly in size with the season of the year. The description immediately following applies to conditions existing in the autumn just before the onset of dormancy.

An ordinary section of the hibernating gland of a woodchuck killed in the fall of the year is illustrated in figure 8. Figure 12 gives more details due to special technique and higher magnification. These large polygonal cells, highly laden with fat and lipoids, are from 26 to 34μ in diameter and contain a nearly spherical nucleus slightly under 6μ in diameter, after ordinary fixation (formalin-corrosive sublimate) and paraffin embedding. The irregularities in the nucleus appear to be produced by pressure from the surrounding fat globules, for when some of the fat is absorbed, as in figure 11, the nucleus appears much more nearly spherical. The chromatin forms a dense, coarse, granular network, sufficiently open, however, to reveal a distinct nucleolus within. The round form of these nuclei as well as their position distinctly within the margins of the cells make their identification comparatively easy even with the simplest technique. One wonders why anyone should confuse them with the endothelial nuclei of the capillaries, as was done by Hirsel and Frey ('63).

The cell body contains one and occasionally two large fat globules and many smaller ones of various sizes, as is illustrated especially in figure 12. The nucleus is therefore very eccentric in position, in contrast with the white rat (figs. 17 and 18) where most of the cells are filled with only the small droplets so that the nucleus usually remains more centrally located. The nucleus is, however, never flattened much if at all no matter how fat the animal is. Thin sections from material in which the fat and lipoids have been preserved and stained with osmic acid (or Sudan III) gives the appearance shown in figure 13 where each compact group of black spots represents the fat within a single cell.

Between the fat globules is a considerable amount of highly granular cytoplasm. The granules are closely packed and spherical. Most of them are fairly uniform in size (about 1μ in diameter). There are a few larger ones which approach the smaller fat globules in size. Judging from the variable way they stain after uniform chromation, they are variable in composition—possibly due to differences in amount and character of the lipoids present, for they give evidence of containing lipoid. It would take colored plates and extended description of detailed technique to fully justify these statements; but it is altogether probable that they represent different stages in the transformation of some lipoid-containing product. These granules are distinctly larger than the apparently corresponding granules illustrated by Cramer ('20) and which he considers mitochondria. While they are especially well fixed and stained by the usual mitochondrial methods (janus green intra vitam was not tried), they are more easily preserved and stained than is usually the case with mitochondria. There is some indication of the presence of much smaller fuchsinophile granules which may prove to be typical mitochondria. This point, however, needs further investigation.

A comparison of the hibernating gland of the woodchuck with that of other animals detailed in the literature, shows that this tissue is strikingly uniform over a wide range of species both in the size of the whole cell and of the nucleus and in the finer structure. No study of the nerve supply was undertaken at this time since the nerves which seemed to enter the various lobes of the gland apparently passed on through and did not supply visible fibers to the tissue.

Changes during and subsequent to hibernation

That the hibernating gland undergoes a seasonal variation in size and appearance in many hibernating species has been noted by most of the investigators, beginning with Harder in 1686. Prunelle (1811) and Tiedemann (1815) were under the erroneous idea that it decreased in summer (from $\frac{1}{24}$ to only $\frac{1}{160}$ of the body weight, according to Tiedemann), evidently due to having compared the condition of early dormancy with that existing late in the spring before fat had accumulated again, for all careful observations show that it decreases continuously during winter-sleep. This decrease in size is accompanied by an increase in the intensity of the brown color. Valentine ('57 and '59) calculated the loss sustained by it and other tissues of the body in three marmots. His figures show that at the beginning of dormancy the hibernating gland constitutes 1.33 per cent of the net body weight (total weight minus urine and contents of alimentary tract), while at the end of winter-sleep it constitutes only 0.68 per cent, having lost 68.79 per cent of its original weight. Ordinary adipose tissue lost 99.31 per cent of its initial weight during the same time. Since ordinary adipose tissue constituted 17.05 per cent of the net body weight at the beginning of dormancy, it follows that to every 17 grams of ordinary adipose tissue used up only about 0.9 gram of hibernating gland tissue was metabolized. A certain portion of the loss sustained by other parts of the body was undoubtedly due to a loss of adipose tissue that could not be dissected out. Hence ordinary adipose tissue contributed about twenty times as much food material as did the hibernating gland. Similar calculations on other organs indicate that the skeletal muscles contributed eight times and the liver twice as much material for food as did the hibernating gland. This is also borne out by his figures on the average daily loss per day of the various parts of the body, the average daily loss of the hibernating gland per kilogram of body weight being 0.08 gram after 44 days of dormancy and 0.05 gram after 163 days of winter-sleep.

Carlier ('93) and Carlier and Evans ('03) made the most extensive study so far reported. Carlier found that in the hedgehog at the beginning of winter-sleep it equals about 3.04 per cent of the body weight, but it diminishes rapidly during the early part of hibernation so that at the beginning of January it equals only 1.5 per cent. At the end of March it has decreased to 0.9 per cent. After the animal wakes up the organ decreases rapidly, till by the beginning of June it is reduced to a few fibrous cords. By the end of June it commences to increase in size. His description of the entire disappearance of most of the cells during the decrease could not be verified by such careful workers as von Hansemann ('02) and Auerbach ('02), who also studied the hedgehog. Carlier found no evidences of phagocytosis. His first impression was that as the gland decreased the fat was converted into a non-fatty material and did not undergo simple atrophy as in ordinary adipose tissue, as was maintained by Ehrmann ('83); but later ('03), in connection with Evans, about thirty more hedgehogs were investigated and this notion discarded. They found upon chemical analysis of the hibernating gland that the amount of water varied inversely as the amount of fat, the latter apparently being partly replaced by water during the inanition period. This supports Aeby's ('75) findings on the marmot where during the later stages of dormancy the hibernating gland had a smaller percentage of solids (hence more water) but a larger percentage of ash than at the beginning. They also found that the amount of proteins varied less than one per cent. Phosphorus decreased rapidly during the first month of winter-sleep, then there was no further decrease.

Von Hansemann ('02) made measurements on the size of the fat-containing cells in autumn and again in February and showed that the decrease which takes place in these cells and in the whole organ can be accounted for by the loss of fat. And similarly the enlargement of the hibernating gland is apparently due merely to the accumulation of fat. No mitotic figures were ever observed in adult animals during enlargement of the organ. He found no seasonal change in the hibernating gland of non-hibernating animals, like the rat, provided they remain equally well nourished.

As is the case with other hibernating animals, all parts of the hibernating gland of the woodchuck slowly decrease in size and become darker in color during winter-sleep, which in this species is characterized by almost continuous torpor for over three months during which no food or water is taken into the system. A few times during this period they become active enough to slowly crawl about; but the body temperature rarely goes above 15°C. and is frequently as low as 6°C., whereas the normal temperature during summer activity is 37°C. This decrease in size is due apparently to the loss of fatty material. Figure 11 gives a general idea of the cellular appearance well along in the dormant period (February 16th). When compared with figure 8 it is evident that the large fat droplets (indicated by vacuoles) have decreased in size and number, but there are so many small ones left that the large cell body has a mottled appearance. The cells in this particular case average only 24μ in diameter, as compared with 30μ before hibernation.

The nucleus becomes more nearly round and is seen more distinctly. The average diameter has increased slightly to 6μ. Embedded material gives the impression, therefore, that a distinct increase in the volume of the nucleus has taken place; but this is apparently exaggerated by the shrinkage taking place during fixation and embedding, which makes the nuclei of cells that are greatly distended with fat more angular than they really are. Frozen sections of formalin material indicate only a slight degree of irregularity in the shape of the nuclei before dormancy. There is no observable change in the structure of the nucleus.

At the end of hibernation and before the animal has become very active (within a day after waking up) the gland may still constitute 2 per cent of the body weight, which is its relative weight before the onset of dormancy, indicating that its loss has been about the same as that of the body as a whole. Apparently in other animals, judging from the literature, the loss is relatively greater than in the woodchuck; but it is not always clear just how soon after waking up the animals have been sacrificed. This is an extremely important fact because upon becoming active the rate of tissue loss is increased many fold. Since the body weight has fallen 25 per cent during winter-sleep it follows that the hibernating gland has lost about 25 per cent of its original weight. Ordinary adipose tissue has decreased relatively much faster having by this time lost from two-thirds to three-fourths of its weight. So there is, as maintained by Valentine ('57), Hammar ('95), Cramer ('20) and others, a distinct difference in the percentage loss in the two types of fatty tissue which to some extent, as explained later, one would expect from the differences in the composition of these tissues.

With the onset of bodily activity, incident to the breeding season, and for a period of three to four weeks before food is available, the body weight decreases much more rapidly, till there is a loss of 35 per cent. Ordinary adipose tissue is rapidly absorbed till only a trace is left. All the lobes of the hibernating gland decrease more rapidly than during winter-sleep and more rapidly than the body as a whole; but not to the extent that occurs in ordinary adipose tissue nor to the degree indicated by Carlier ('93) in the hibernating gland of the hedgehog. There is no evidence in the woodchuck of the entire cell degeneration pictured by Carlier. None of the nuclei show pyknosis, karyorrhexis, karyolysis or other signs of morbid destruction. The gland now reaches a minimum where it represents only 0.7 to 0.8 per cent of the body weight, as is well illustrated in figure 7, which should be compared directly with figure 6 and which is from an animal killed April 18th, after four weeks of activity. Figures 6 and 7 are transverse sections through the thickest part of the superior mediastinal lobe as determined by complete serial section of the entire mediastinal contents. The level shown in figure 7 is only slightly above the aortic arch, which is traversed by the level shown in figure 6. As seen from the cross section of the trachea, especially, the two animals compared are about the same size (the one in figure 6 weighed 3130 grams and the one in figure 7 weighed 2772 grams before the onset of hibernation). The greatest change by far in this lobe is, however, in the transverse diameters. Incidentally the walls of the oesophagus show a marked reduction in thickness in figure 7. The entire hibernating gland has lost, in round numbers, 75 per cent of its original weight.

From the histological picture, as shown in figure 9, it is clear that each cell retains much of the granular cytoplasm while the fatty materials have been largely absorbed. The cells are now only 8 to 15μ in diameter and much more irregular in shape. The nucleus remains perfectly normal in appearance and shows no change in size or structure.

Fat is never entirely absent from the tissue. In figure 9 numerous small and some medium-sized globules are seen as vacuoles to the right and below the center of the photograph. Figure 14 is a positive picture of the fat left in an animal that had been awake several weeks (killed April 29th). The fat has been blackened with osmic acid. In stain, magnification, and thickness of section, figure 14 is directly comparable with figure 13, which illustrates the fat present before dormancy. It must be remembered, however, that since the cells have been reduced to one-third their original diameter, figure 14 in terms of cell diameter is relatively three times as thick and in area shows nine times as many cells as in figure 13. It is, therefore, entirely probable that the total loss in weight of 75 per cent which the hibernating gland may normally sustain in the spring before it begins to increase again, can be largely accounted for by loss of fat alone due to the large proportion of the total cell volume which is fat and the great reduction in the size of the cell which results from a loss of nearly all this fatty material, as was maintained especially by von Hansemann ('02).

From the weight of the separate lobes it appears that all undergo about the same relative reduction. They are all essentially alike in histological structure at any stage. Within a given lobe and even within a particular lobule there are variations in that all the cells are not exactly in the same stage of reduction. This is indicated in figure 9 which shows that the cells with the most abundant cytoplasm are at the margin (marked *M*) of the lobule while the region about the blood vessel shown in the lower part of the photograph is richer in fat as if there were a mobilization of fat towards the vessel. But these differences are relatively minor.

The statement of Malesani ('02) that the hibernating gland loses its glandular aspect in March at the close of hibernation is difficult to interpret since from the histological appearance (fig. 9) one would say that just the reverse is true.

COMPARISON OF THE HIBERNATING GLAND WITH ORDINARY ADIPOSE TISSUE

A thoroughgoing discussion of the relation between ordinary adipose tissue and the hibernating gland is impossible at this time due to the lack of reliable biochemical and microchemical studies directed along this line. A number of observations bearing upon the subject may, however, be worthy of examination.

According to structure, it is clear from the illustrations accompanying this paper and all descriptions of reliance found in the literature on other forms that the fat containing cells of the two tissues are distinctly different. In regard to size the cells of the hibernating gland are much smaller, being regularly one-half the diameter of adipose cells in the woodchuck. The amount of fat and its arrangement within the cell is different. The hibernating gland cell, no matter how fat the animal (and as much as 26 per cent of the body weight before hibernation in the woodchuck may be dissectible adipose tissue), is always polylocular in well-nourished animals, which recalls the failure of Hammar ('95) to produce unilocular cells resembling ordinary adipose cells out of hibernating gland cells by overfeeding rats for three months on a diet rich in fat. Carlier and Evans ('03) similarly showed that the maximum amount of fat obtainable from the hibernating gland of the hedgehog was 40 per cent, as compared with 90 per cent often obtainable from ordinary adipose tissue. Shattock ('09), while claiming that he found more fat in the hibernating gland than indicated by Carlier, states that he found distinctly less than in a similar weight of subcutaneous adipose tissue of the same animal.

Chemical differences in the fat has not been thoroughly investigated. Engelmann, according to Salmon ('10, p. 89), found the gland especially rich in labile lipoid, probably lecithin. Shattock ('09) found that the iodine value of the fat from the hibernating gland was 96.3 to 100, that of the subcutaneous tissue of the same animal was 90 to 92.5. Vignes ('13) merely states that in the rat the fatty material in the hibernating gland is composed largely of a substance soluble in chloroform and ether, but insoluble in acetone and apparently closely related to lecithin, probably jecorin. Cramer ('20) similarly emphasizes the presence of considerable cholesterin compounds and other lipoids in addition to true fat. In the hibernating gland of the hedgehog Carlier and Evans ('03), however, found that 90 to 91 per cent of the fat was olein, the remainder being stearin with a trace of palmatin, lecithin, and pigment. Lecithin was inferred from the presence of phosphorus. The olein was used up faster than the other fats during winter and spring.

According to Carlier and Evans, the pigment which apparently was not metabolized, appeared to be a lipochrome which they could not completely separate from the fat. It was soluble in toluol, turpentine, chloroform, petroleum, essential oil, and to a certain extent in alcohol; but was insoluble in solvents miscible with water, such as ethyl acetate, acetic acid and glycerol. The lead salts of the pigment was soluble in ether. However the presence of pigment is not peculiar to the hibernating gland for ordinary adipose tissue also contains a yellow pigment, which, just as that in the hibernating gland, is absorbed less rapidly than the fat, as is evident from the darker color of subcutaneous fat in emaciated subjects.

It may be noted here that Carlier and Evans found no carbohydrates in the hibernating gland. Salts were present as phosphates, chlorides and sulphates of sodium and potassium. There was a little magnesium and a trace of calcium and aluminum. Sodium chloride was most abundant, while sulphates were found only in traces.

A most striking difference between the two types of cells is the large amount of coarsely granular cytoplasm in the case of hibernating gland. This accounts for the compact appearance of the hibernating gland in contrast with the open 'lacy' appearance of adipose tissue. This is well brought out, though over emphasized, in figure 10, which is from a woodchuck killed February 16th. But even when the fat is maximal, as in figure 8, the hibernating gland is much more solid in appearance. As might be expected, Carlier and Evans ('03) found that as much as 15 to 16 per cent of the gland was protein. The membrane surrounding the fat in ordinary adipose tissue constitutes only 1.6 per cent (Reinecke, '74, Ludwig-Festschrift, Leipzig). This great difference is primarily due to the abundant cytoplasm in the hibernating gland. These facts must be taken into consideration in evaluating the arguments put forward by Cramer ('20) and others that the two types of fatty tissue are functionally different because they act differently under conditions of restricted diet as was also shown by Hammar ('95) in the rat during starvation and by Valentine ('57), especially, during hibernation of the marmot—ordinary adipose tissue decreasing relatively much more rapidly. This is borne out by the study here reported on the woodchuck and is what one would expect from the fact that there is relatively much more fat in the one than the other, so that if the fats and lipoids decrease at the same relative rate in the two tissues, ordinary adipose tissue would show a greater percentage loss. But even after due allowance for the difference in fatty content, ordinary adipose tissue according to all observations, fluctuates much more than the hibernating gland. The thin film about the fat globule and the more evident perinuclear cytoplasm in even mature adipose cells is not free from granules, since there are at least numerous round mitochondria; but the granules in the hibernating gland of the woodchuck are larger.

The nucleus differs distinctly in the two tissues since there is always a sufficiently wide rim between the largest fat globules and the periphery of the cells in the hibernating gland to leave the nucleus relatively unflattened, in contrast to the very much flattened nucleus of typical mature adipose cells.

There is no evidence in the woodchuck (and very little if any in any other animal) of a transformation of hibernating gland cells to ordinary fat cells, although the latter may be mixed with the former where the two tissues are in contact. Ordinary adipose tissue may partly or entirely surround lobules and irregular masses of the hibernating gland, as shown in figures 10 and 19. Figure 10 gives one the impression that the hibernating gland has invaded the region of the atrophic thymus largely occupied by adipose tissue; but there are no transitional cells indicating that either type has been derived from the other. The cells are either distinctly ordinary adipose cells or distinctly those of the hibernating gland, as far as could be determined by a careful examination of abundant material fixed in various solutions (formalin for frozen sections, formalin and corrosive sublimate, Zenker's neutral formalin and potassium dichromate, various fixers containing osmic acid) and stained by several methods (Sudan III, osmic acid, hematoxylin and eosin, iron alum, hematoxylin, acid fuchsin and methyl green).

In the final stages of the inanition that occurs during and just subsequent to hibernation the two types of cells are distinctly different. True adipose cells are generally regarded as reverting to ordinary connective tissue cells, while those of the hibernating gland (even after there has been a loss of as much as 40 per cent of the body weight) retain relatively an abundant amount of cytoplasm and the usual large spherical nucleus.

SUMMARY

1. The present status of the so-called hibernating gland, especially with reference to its glandular character, is considered because of the repeated suggestion that it may produce an internal secretion.

2. Its structure as described in the literature is surprisingly alike over a wide range of species both in hibernating and in non-hibernating forms.

3. The presence or absence of the various lobes in at least fifty-five species mentioned by over fifty investigators is tabulated. The table shows that the locations most often mentioned as the site of the organ are the intrathoracic (mediastinal) and cervical. The axillary and interscapular come next; then the perirenal; while the inguinal (along iliac vessels) is least.

4. The views as to the presence of a homologous structure in man are examined with the conclusion that there is no very good evidence in the literature for the idea that the dorso-cervical, axillary, or perirenal adipose tissue is modified hibernating gland

tissue, for in animals with a typical hibernating gland there is in these locations also ordinary adipose tissue; but a variable amount of multilocular fat cells essentially like those in a typical hibernating gland may occasionally be present in the perirenal fat of human infants.

5. The literature on the embryology of the hibernating gland is very meager. From the information available it appears to arise from young connective tissue which appears very much like the so-called primitive fat organ.

6. The essential literature is reviewed with respect to the significance of this organ. This history reveals at least three periods. Up to the early part of the nineteenth century (and occasionally somewhat later) it was generally regarded as a part of the thymus. Then followed a period during which it was usually recognized as a separate organ of the hemopoietic group. During the last sixty years, but also occasionally before this, it has quite generally been looked upon as a modified form of adipose tissue serving merely as a storage of food material. However, now and then its internal secretory character has been stressed.

7. The hibernating gland of the American marmot (Marmota monax rufescens) is described. This American species differs from the European marmot in that there is no hibernating gland tissue in the abdominal cavity of the woodchuck. The histological features are given in detail.

8. Changes in the gland during dormancy are shown to be slower in the woodchuck than in the other animals for which there are data; but subsequent to hibernation and before food is plentiful, the usual rapid loss in weight is noted till it reaches 0.7 to 0.8 per cent of the body weight as compared with 3 per cent before lethargy set in; 75 per cent of the gland is thus finally lost. The cells decrease from 30μ in diameter to 10μ. The nucleus increases slightly in size, especially as judged from embedded material, when fat commences to be absorbed from the cell with the onset of torpor; but there are no changes after this apparent initial increase.

9. A comparison between the hibernating gland and ordinary adipose tissue indicates that the chief cells of the two tissues are distinct types and that one is not transformed into the other. This in general is borne out by other investigators.

10. The structural differences, such as the more granular character of the cytoplasm of the cells, the higher lipoid but lower fat content, as well as the relatively slower rate of loss in weight (during restricted diet) of the hibernating gland, as compared with ordinary adipose tissue, are not sufficient evidence to warrant the conclusion that the structure under consideration is of any endocrine significance except in such a general sense as would also include ordinary adipose tissue (Gley, '17). The pathological evidence, as well as the purely physiological, is too meager to indicate at all clearly its rôle.

11. As a special source of reserved food to help the organism weather long periods of inanition, it was shown to contribute only about one-thirtieth (calculations from the figures given by Valentine) to at most one-twentieth (data from the woodchuck) of the total weight of the tissues lost. Other organs, not primarily composed of storage tissues, supply much more material than the hibernating gland. That it contributes some special food elements—a particular vitamine, for example—is of course possible; but that it does so has never been demonstrated. There is no reason why the other tissues of the body that yield up their substance do not also contribute these essential constituents.

12. Until the nature of this structure is better understood, it would seem unwise to discuss the relative merits of the various terms applied to it. Hibernating gland has been used here merely because this is the most generally used term and not because the writer believes that it is a gland in any strict sense, nor that it has any special significance during hibernation. Possibly multilocular adipose tissue would be the least objectionable.

BIBLIOGRAPHY

Aeby, C. 1875 Arch. f. exper. Path. u. Pharmakol. (Leipzig), Bd. 3, S. 180.

Afanassiew, B. 1877 Arch. f. mikr. Anat. (Bonn), Bd. 14, S. 375.

Auerbach, M. 1902 Arch. f. mikr. Anat. (Bonn), Bd. 60, S. 291.

Ballowitz, E. 1891 Anat. Anz. (Jena), Bd. 6, S. 135.

Barkow, H. C. L. 1846 Der Winterschlaf nach seinen Ercheinungen im Thierreich dargestellt (Berlin), chap. 16.

Bell, E. T. 1909 Am. Jour. Anat. (Philadelphia), vol. 9, p. 412.

Bensley, B. A. 1918 Practical anatomy of the rabbit (Toronto and Philadelphia,) 2nd ed., p. 26.

Berg, W. 1910–11 Ztschr. f. Morph. u. Anthrop. (Stuttgart), Bd. 13, S. 305.

Bonnot, E. 1908 Jour. Anat. and Physiol. (London), vol. 43, p. 43.

Buffon, G. L. L. 1749 Oeuvres avec des suppléments augmentées de la classification de G. Cuvier (Paris, 1835), T. 5, p. 226.

Burdach, K. F. 1830 Die Physiologie als Erfahrungswissenschaft (Leipzig), Bd. 3, S. 510.

Carlier, E. W. 1892–93 Jour. Anat. and Physiol. (London), vol. 27, p. 508.

Carlier, E. W., and Evans, C. A. L. 1903–04 Jour. Anat. and Physiol. (London), vol. 38, p. 15.

Charpy, A. 1901 Traité d'anatomie humaine (Poirier-Charpy) (Paris), T. 2, p. 427.

1907 Bibliographie anatomique (Paris and Nancy), T. 16, p. 207.

Cramer, W. 1920 Brit. Jour. Exper. Path. (London), vol. 1, p. 184.

Curling, T. B. 1850 Med.-Chir. Trans. (London), vol. 33, p. 303.

Cushing, H., and Goetsch, E. 1915 Jour. Exper. Med. (New York), vol. 22, p. 25.

Dubois, R. 1896 Physiologie Comparée (Paris), pp. 225 and 94.

Ecker, A. 1853 Wagner's Handwörterbuch der Physiologie (Braunschweig), Bd. 4, S. 121.

Ehrmann, S. 1883 Sitzungsb. d. k. Akad. d. Wissensch., (Wien.) Math. Naturw. Classe, Abteil. 3, Bd. 87, S. 88.

Fagge, H. 1871 Med.-Chir. Trans. (London), vol. 54, p. 154.

Fleischel, E. 1869 Sitzungsb. d. k. Akad. d. Wissensch., (Wien) Math. Naturw. Classe, Abteil. 2, Bd. 60, S. 60.

Friedleben, A. 1858 Die Physiologie der Thymusdrüse (Frankfurt a. M.), Abschnitt 10, S. 102.

Gley, E. 1917 The internal secretions (New York), pp. 90, 134, 172–174.

Hammar, J. A. 1895 Arch. f. mikr. Anat. (Bonn), Bd. 45, S. 512.

Hansemann, D. (von) 1902 Arch. f. Anat. u. Physiol., Physiol. Abt. (Leipzig), S. 160.

Harder, J. J. 1686 Ephemerid. acad. nat. cur., Ann. 4, Dec. 2, obs. 122.

Hatai, S. 1902 Anat. Anz. (Jena), Bd. 21, S. 369.

Haugstedt, F. C. 1831 Thymi in homine ac per seriem animalium descriptionis anatomico-physiologiscae particula prior (Hauniae), p. 28.

Hirsel, H., und Frey, H. 1863 Ztschr. f. wissensch. Zool. (Leipzig), Bd. 12, S. 165.

Horvath, A. 1878–1881. Verhandl. d. phys. med. Gesellsch. (Würzburg), N. F., Bd. 12–15.

Howell, A. H. 1915 Revision of the American marmots. North American Fauna, No. 37, U. S. Dept. of Agriculture, Bureau of Biological Survey, Washington, D. C.

Jacobson, L. 1817 Deut. Arch. f. d. Physiol. (Halle), Bd. 3, S. 151.

Jones, C. H. 1852 Todd's Cyclopaedia of Anat. and Physiol. (London), vol. 4, p. 1095.

Leydig, Fr. 1857 Lehrbuch der Histologie (Frankfurt a. M.), S. 431.

Long, J. A. 1922 Anat. Rec. (Philadelphia), vol. 23, p. 107.

Malesani, L. 1902 (Cited by Salmon, La Fonction du Sommeil, p. 89.)

Mangili, G. 1807 Annales du muséum d'histoire naturelle (Paris), T. 9, p. 106.

Mann, F. C. 1916 Am. J. Physiol. (Baltimore), vol. 41, p. 173.

Meckel, J. F. 1806 Abhandl. aus der mensch. u. vergleich. Anat. u. Physiol. (Halle), Bd. 8, S. 1.

1815 Deut. (Meckel's) Arch. f. d. Physiol. (Halle), Bd. 1, S. 493.

Merkel, F. 1899 Topographische Anatomie (Braunschweig), Bd. 2, S. 27.

Mietens, H. 1908 Jenaische Ztschr. f. Naturw. (Jena), Bd. 44, S. 149 (especially pp. 171–176).

Owen, R. 1868 On the anatomy of vertebrates (London), vol. 3, p. 568.

Pallas, P. S. 1778 Novae species quadrupedum e glirium ordine. (Erlangen).

Polimanti, O. 1912 Il Letargo (Roma), p. 46.

Poljakoff, P. 1888 Arch. f. mikr. Anat. (Bonn), Bd. 32, S. 155.

Prunelle, C. F. V. G. 1811 Annales du museum d'histoire naturelle (Paris), T. 18, p. 302.

Rudolphi, K. A. 1830 Grundriss der Physiologie (Berlin, Reutlingen, J. J. Mäcken'schen Buchhandlung), Bd. 1, S. 244.

Salmon, A. 1910 La Fonction du Sommeil (Paris), pp. 88 and 163.

1916 Lo Sperimentale (Florence), T. 70, S. 345.

Scammon, R. E. 1919 Anat. Rec. (Philadelphia), vol. 15, p. 267.

Scheuczer, J. J. 1727 Phil. Trans. (London), vol. 34, S. 237; ibid., abridged by Eames and Martin, vol. 7, p. 453.

Shattock, S. G. 1908–9 Proc. Roy. Soc. Med. (London), vol. 2, Part 3, Pathological Section, p. 207 (particularly p. 252).

Shaw, H. Batty 1902 Jour. Anat. and Physiol. (London), vol. 36, p. 1.

Simon, J. 1845 A physiological essay on the thymus gland (London), p. 46.

Stannius, H. 1853 Beobachtungen über Verjungungsvorgänge im thierischen Organismus (Rostock and Schwerin).

Sulzer, F. G. 1774 Versuch einer Naturgeschichte des Hamsters (Göttingen).

Tiedemann, F. 1815 Deut. (Meckel's) Arch. f. d. Physiol. (Halle), Bd. 1, S. 481.

Valentine, G. 1857 Untersuchungen zur Naturlehre des Menschen und der Thiere (von Jac. Moleschott) (Frankfurt a. M.), Bd. 2, S. 12; ibid., 1859, Bd. 5, S. 259.

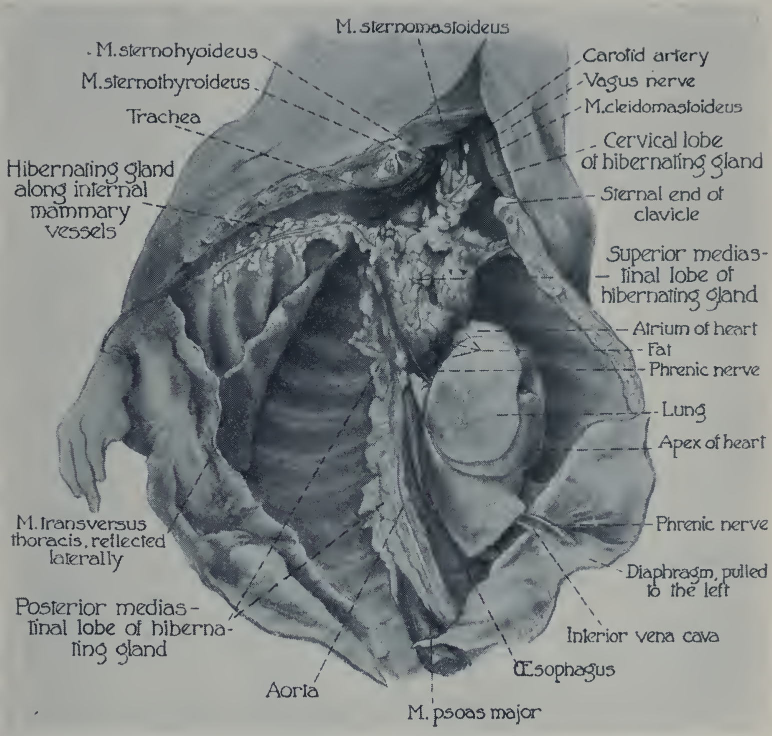
Velsch, G. H. 1670 Ephemerid. acad. nat. cur. Ann. 1, Dec. 1, obs. 160, p. 298.

Vignes, H. 1913 Compt. rend. Soc. de biol. (Paris), T. 75, pp. 360, 397 and 418.

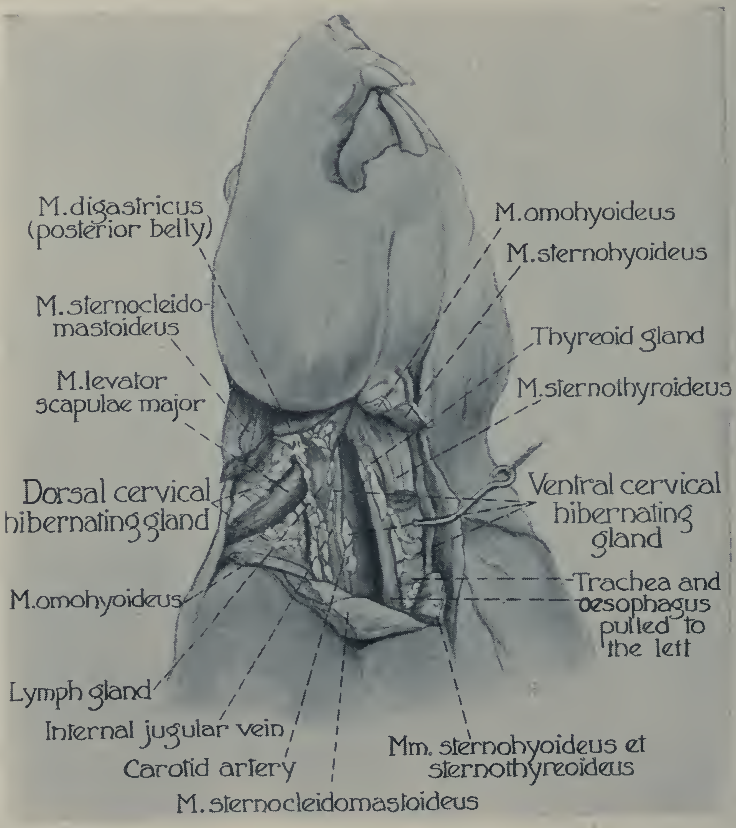
Vogt, C., und Yung, E. 1889–1894 Lehrbuch der praktischen vergleichende Anatomie (Braunschweig), Bd. 2, S. 955.

Wagner, R. 1834–35 Lehrbuch der vergleichenden Anatomie (Leipzig), p. 253.

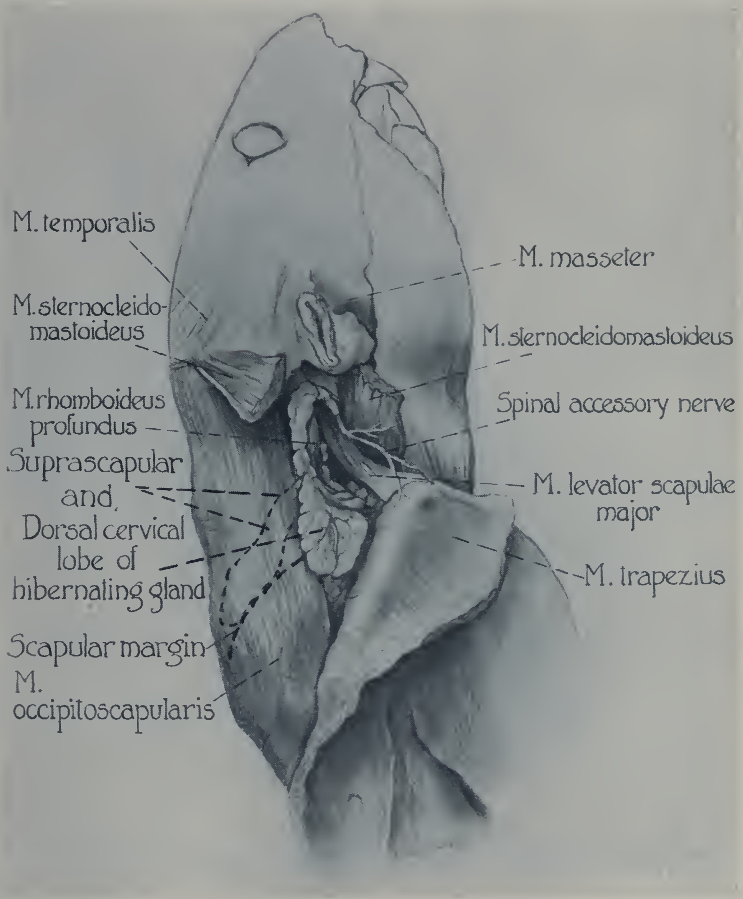
Wiedersheim, R. 1907 Comparative anatomy of vertebrates, 3rd ed. (founded on the 6th German edition, by W. N. Parker) (London), p. 435.


M. sternomastoideus
M. sternohyoideus
M. sternothyroideus
Trachea
Hibernating gland along internal mammary vessels
Carotid artery
Vagus nerve
M. cleidomastoideus
Cervical lobe of hibernating gland
Sternal end of clavicle
Superior mediastinal lobe of hibernating gland
Atrium of heart
Fat
Phrenic nerve
Lung
Apex of heart
M. transversus thoracis, reflected laterally
Phrenic nerve
Diaphragm, pulled to the left
Posterior mediastinal lobe of hibernating gland
Inferior vena cava
Œsophagus
Aorta
M. psoas major

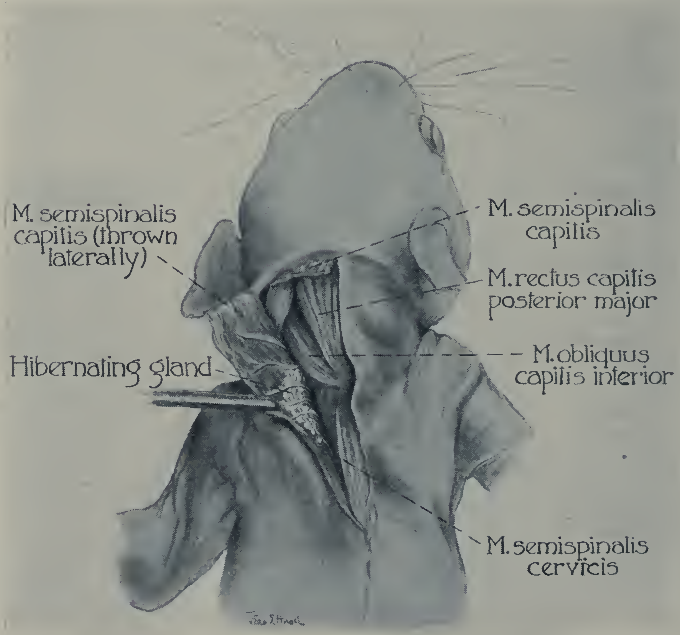
1 Intrathoracic portion of hibernating gland of adult woodchuck exposed by longitudinal incision just lateral to left margin of sternum, forceful retraction of chest walls and reflection of the heart and right lung to the left.


M.digastricus (posterior belly)
M.sternocleido-mastoideus
M.levator scapulae major
Dorsal cervical hibernating gland
M.omohyoideus
Lymph gland
Internal jugular vein
Carotid artery
M.sternocleidomastoideus
M.omohyoideus
M.sternohyoideus
Thyreoid gland
M.sternothyroideus
Ventral cervical hibernating gland
Trachea and oesophagus pulled to the left
Mm. sternohyoideus et sternothyreoideus

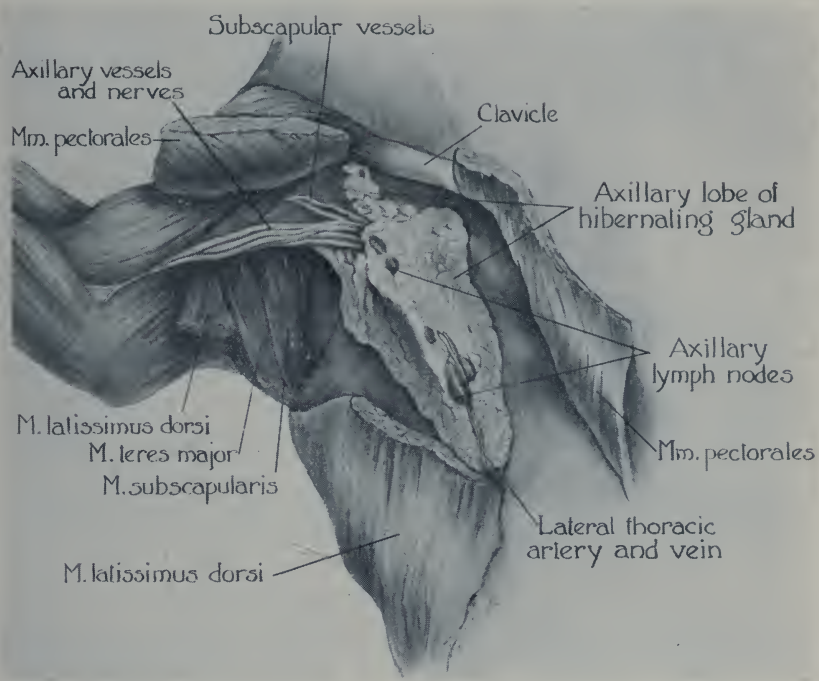
2 Cervical portion of hibernating gland of adult woodchuck as seen from ventrolateral aspect. Only three of the numerous more ventrally placed masses are labeled.


M. temporalis
M. sternocleido-mastoideus
M. rhomboideus profundus
Suprascapular and Dorsal cervical lobe of hibernating gland
Scapular margin
M. occipitoscapularis
M. masseter
M. sternocleidomastoideus
Spinal accessory nerve
M. levator scapulae major
M. trapezius

3 Cervical portion of hibernating gland of adult woodchuck viewed from a lateral exposure. One dorsal lobe is not exposed, its position being merely outlined.


M. semispinalis capitis (thrown laterally)
Hibernating gland
M. semispinalis capitis
M. rectus capitis posterior major
M. obliquus capitis inferior
M. semispinalis cervicis

4 Developing hibernating gland in young woodchuck. Shows position of the most dorsal part of the hibernating gland of the neck region.



5 Axillary lobe of hibernating gland of adult woodchuck. Front leg has been forcibly retracted backward.

PLATE 6

EXPLANATION OF FIGURES

6 Photograph of transverse section through superior mediastinal contents of an adult woodchuck, killed August 20th, showing typical hibernating gland and its relations before hibernation. Zenker's fixation, 30μ, hematoxylin and eosin. × 2.

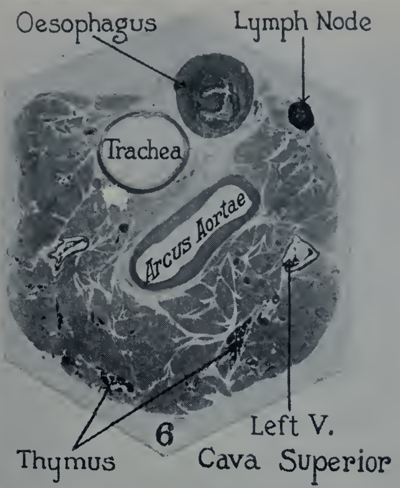
7 Photograph of transverse section through superior mediastinal contents of an adult woodchuck, killed April 18th, showing the great reduction that may occur before food is available in the spring, when compared directly with figure 6. Same technique and magnification as figure 6.

8 Photograph of a section of hibernating gland of woodchuck killed October 25th, when fatty contents of cells are maximal. Vacuoles represent fat and lipoid globules dissolved out. Formalin-corrosive sublimate fixation, 5μ, hematoxylin and eosin. × 200.

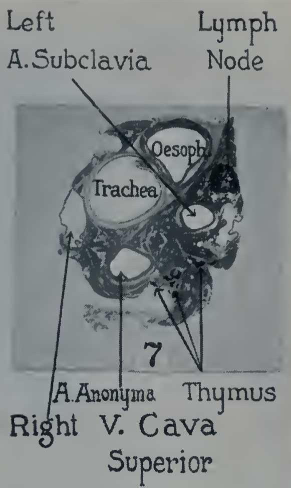
9 Photograph similar to that in figure 8 from the hibernating gland when minimal. Same animal from which figure 7 was obtained, killed April 18th. A small amount of fat is indicated by the vacuoles especially prominent below and to the right of the center near a small artery. Cell body greatly reduced in size. *M* indicates margin of lobe. Same technique and magnification as figure 8.

10 Photograph of section through superior mediastinal lobe of hibernating gland of adult hibernating woodchuck, killed February 16th, to illustrate relation of adipose tissue of atrophic thymus to hibernating gland. Formalin-corrosive sublimate fixation, 5μ, hematoxylin and eosin. × 30.

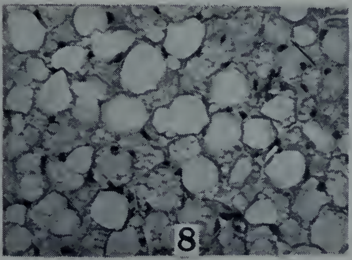
11 Retouched photograph of section of hibernating gland of adult woodchuck during hibernation (February 16) especially to show the rich vascular system which is brought out sharply. It also illustrates an intermediate condition between that found before hibernation (fig. 8) and that which follows hibernation (fig. 9). Medium-sized globules of fat and many smaller ones appear as vacuoles in the cells. Same technique and magnification as in figures 8 and 9.


Oesophagus
Lymph Node
Trachea
Arcus Aortae
Thymus
Left V. Cava Superior

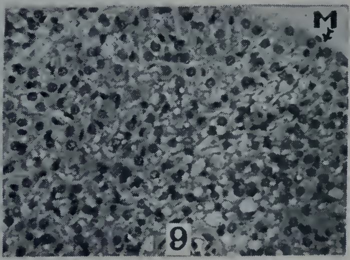
6


Left A. Subclavia
Lymph Node
Oesoph.
Trachea
A. Anonyma
Thymus
Right V. Cava Superior

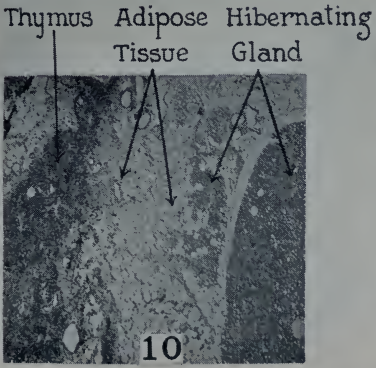
7



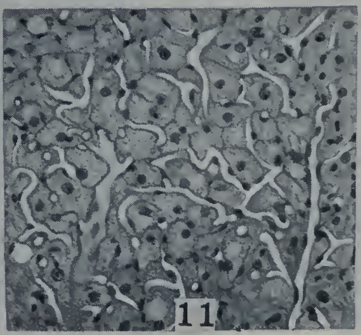
8


M

9


Thymus
Adipose Tissue
Hibernating Gland

10



11

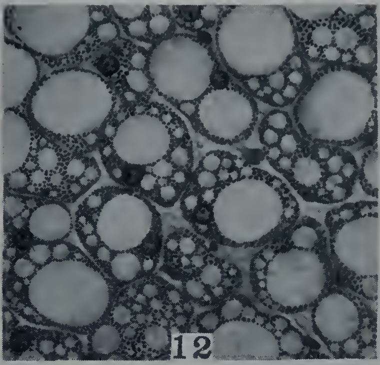
PLATE 7

EXPLANATION OF FIGURES

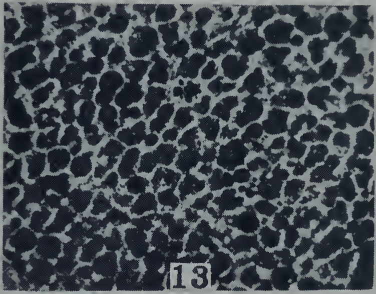
12 Retouched photograph of a section of the hibernating gland with cells maximal in size, showing detailed structure. Fatty contents appear as vacuoles. Numerous secretion-like granules fill the cytoplasm. Neutral formalin and potassium dichromate fixation, 4μ, acid fuchsin and methyl green. × 500.

13 Photograph of a section of hibernating gland showing maximal fatty content, which has been blackened by osmic acid. Each cell appears as a closely packed group of black spots. Animal killed October 14th. Meves' acetic-osmic-chromic acid fixation, 5μ, no stain. × 112.

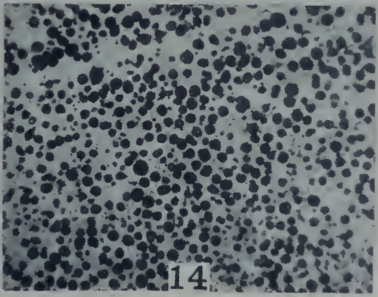
14 Photograph similar to figure 13, but from an animal killed April 29th, in which the hibernating gland was greatly reduced. Many cells still contain a medium-sized fatty globule and occasionally small ones. Same technique and magnification as in figure 13.



12



13



14

PLATE 8

EXPLANATION OF FIGURES

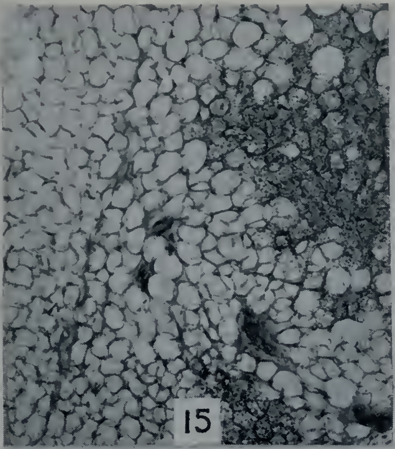
15 Photograph of a section of perirenal adipose tissue of a human infant showing two groups of multilocular fat cells (recognized by their dense appearance in the midst of ordinary unilocular adipose tissue. Zenker's fixation, thick celloidin section, hematoxylin and eosin. × 80.

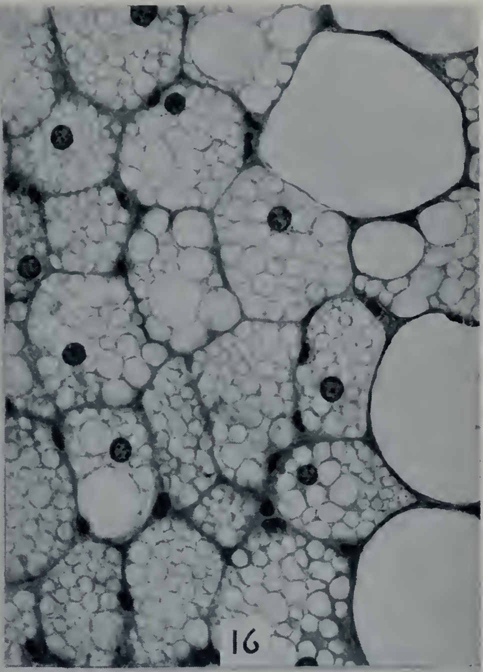
16 Retouched photograph (using under-exposed print for outline) of a small area of the multilocular adipose tissue shown in figure 15 under higher magnification showing the nuclear and general cytoplasmic structures of the cells, which are to all appearances identical with those found in many animals (e.g., white rat, illustrated in figs. 17, 18, and 19). One whole cell and parts of three other ordinary adipose cells included for comparison. × 500.

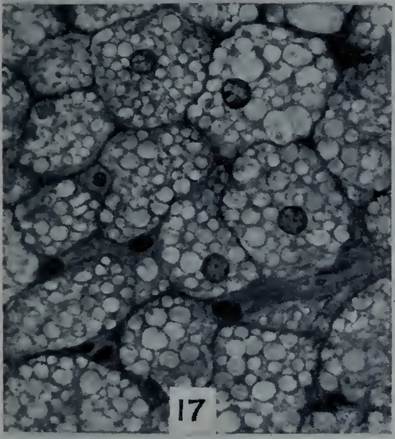
17 Retouched photograph of a section through the brown multilocular adipose tissue from the region of the common iliac vessels of a fat adult white rat showing cells which are indistinguishable from those which constitute the brown fat or hibernating gland in other typical locations (e.g., axillary region as shown in fig. 18) in this same animal. Zenker's fixation, 5μ, hematoxylin and eosin. × 500.

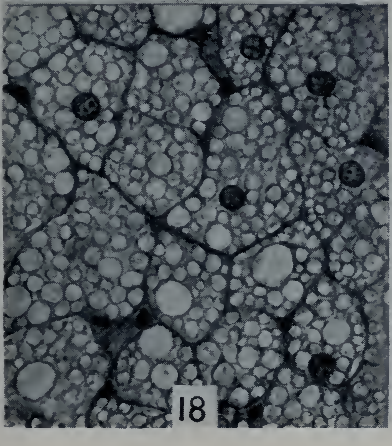
18 Retouched photograph of the axillary hibernating gland, from the same animal as in figure 17, showing the general characteristics of the multilocular fat cells. Same technique and magnification as in figure 17.

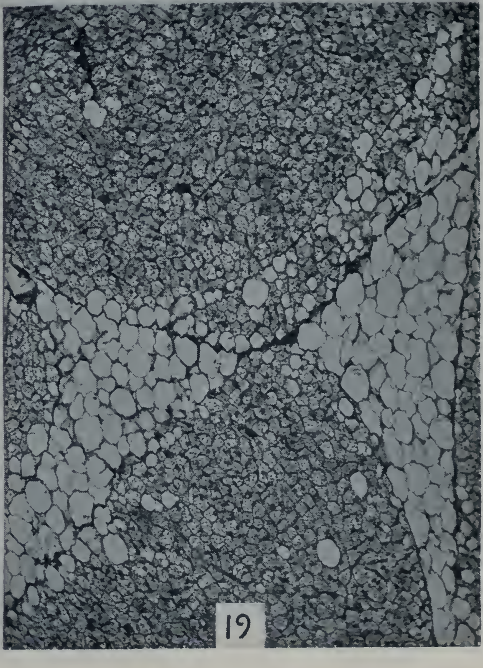
19 A low-power photograph of a section through the interscapular lobe of the hibernating gland of an adult white rat, showing the general tendency for the lobules to be bordered by a variable amount of ordinary adipose tissue. Zenker's fixation, 5μ, hematoxylin and eosin. × 80.


15


16


17


18


19

1

no 20

Reprinted from the Proceedings of the Society for Experimental Biology and Medicine,
1922, xix, pp. 416–423.

206 (1953)

A method for the volumetric study of the human hypophysis cerebri with illustrative results.

By **A. T. RASMUSSEN** and **RUTH HERRICK.**

[*From the Department of Anatomy, University of Minnesota Medical School, Minneapolis, Minn.*]

The importance of the ductless glands in modern medicine has created a demand for more accurate data on these structures. Hammar of Upsala has particularly stressed this point. The need for quantitative facts is more urgent in the case of the hypophysis, or pituitary body, because this organ is composed of several parts which are more or less distinct structurally, functionally and embryologically; and because of the present tendency to classify pituitary disorders from the standpoint of hyper- or hyposecretion of each lobe, the time of onset with reference to adolescence, whether neoplastic or non-neoplastic, etc. The final justification for such a classification of the clinical pictures will depend, at least in a large measure, upon very careful post-mortem analysis of the hypophysis in large series of selected cases. But before pathological material can be properly evaluated it is necessary to establish something of a standard from normal cases, and to determine the range of variability of apparently healthy individuals.

Aside from the gross weight and the length of the three diameters, we have been unable to find on human material anything better than rough qualitative statements and these are greatly at variance with each other. This is particularly true of the relative number and arrangement of the three types of cells in pars anterior and in the amount of colloid. We know of no accurate volumetric data on the size of the various lobes in the hypophysis of man. We have, therefore, set out to determine the relative and absolute weight of the three principal parts of the main body of the gland and of the large colloid masses, together with the relative number and arrangement of the three types of cells in pars anterior of normal adult males between 20 and 60 years of age. For this material we are greatly indebted to the department of pathology, University of Minnesota.

Having made sufficient determinations to establish a comparatively simple routine method applicable to material obtained during regular autopsies, we are summarizing the method that others may profit by our efforts.

METHOD.

After trying various fixing fluids, we found that none were better than ordinary formalin, 15 to 30 per cent. in strength. If detailed work on the cytoplasmic granules is contemplated, the formalin may be neutralized with magnesium carbonate and the tissue chromated after the preliminary formalin fixation. For all general purposes, chromation is unnecessary. The advantage of formalin is that it not only admits of a sharp differential staining of the cells but produces practically no change in the weight of the hypophysis for several hours and but little modification even after several days. It is therefore possible to get the weight of the fresh organ from formalin material, without the necessity of having delicate balances at the autopsy and without delaying fixation.

To avoid injury to the posterior lobe, it is safer to remove the entire sella turcica with the pituitary *in situ* by pinching off the clinoid processes and plunging the entire mass into formalin for later removal of the hypophysis. As soon as possible the excess dural sheath is removed and the infundibular stalk cut off close to the main body of the gland. The organ is again placed in formalin a few moments to moisten the outer surface which becomes somewhat dry as a result of the handling. After blotting off excess formalin the organ is weighed and then fixed three or four days longer in fresh formalin. Without washing in water, the tissue is dehydrated as usual, cleared in xylol and embedded in hard paraffin (60° C.), reducing the duration in the paraffin both to four or five hours by changing the paraffin at least three times.

The organ is cut horizontally, *i.e.*, through its greatest diameter, and not sagittally as in the prevailing method. If one is to depend upon a limited number of sections for an estimate of the condition of the gland, the view obtained in the horizontal plane is by far the best. Mid-sagittal sections are particularly atypical of pars anterior for this region is frequently very poor in eosinophiles. Sections are cut 10 μ till one fourth through the block when an even number (about 10) of 5 μ sections are cut for cytological work and differential cell counting. Cutting at 10 μ is resumed until the middle of the block is reached and again till three-fourths through when similarly a few 5-μ sections are obtained. These division points may be determined near enough by marking the end of the paraffin block after it is trimmed for sectioning.

The whole series is marked off into groups of twenty sections (two 5-μ sections counting as one) and from the middle of each group a 10-μ section is taken. These (usually 30 to 40 in number) can be mounted on three or four slides and stained with Mallory's connective tissue stain (acid fuchsin-aniline blue-orange G) as regularly done in staining connective tissue. Another similar set is taken from points midway between the other series and stained with hematoxylin and eosin in order to have two series which together will constitute a more complete set consisting of every tenth section and also to have a better nuclear stain. Every section of one of these series only (as a rule) is projected at a magnification of twenty diameters upon "American Linen Record" paper (sheets 23 × 36 inches, 72 lbs. per ream) which runs very uniformly at .012 gram per sq. cm. Every sheet needs checking up, however. This is done by cutting out from each corner a square 5 cm. each way and weighing the four squares together. If a heavy sheet is balanced with a light sheet (several sheets being necessary for each determination) the weight per sq. cm. can be kept sufficiently constant. The capsule (including the connective tissue extending in between the lobes), pars anterior, connective tissue trabeculæ and large colloid masses in pars anterior, parenchyma of pars intermedia, colloid in pars intermedia, and pars nervosa are outlined with a hard sharp pencil or with ink. Where the colloid and parenchyma of pars intermedia are very irregularly distributed, it is safer to use both series, thus reducing the error greatly.

These areas are cut out with scissors, using a fine manicuring scissors for cutting out the smaller areas and areas rounded by many sharp turns. The paper representing any particular part is weighed. The percentage that this weight is of the weight of the paper of all parts together constitutes the percentage of the whole organ represented by that part, if the shrinkage is the same for all parts in any particular case.

To determine the shrinkage of the two lobes, they were separated from each other in three cases and each lobe weighed before fixation. The members of each pair were kept together through the entire process of fixation, embedding, etc. From serial sections, as explained above, the final volume was obtained by dividing the total paper weight of a lobe by the weight of one sq. cm. of paper, then dividing the results by the actual magnification (magnification in diameter squared) and finally multiplying by 200 μ (20 × 10 μ) reduced to cm. (.02 cm.). The original volume (before fixation) was determined by dividing the weight by the specific gravity.

The results are tabulated in Table I, from which it is seen that there is sufficiently close agreement between the shrinkage of the two parts in each case that it may be considered the same despite the great difference in structure.

TABLE I.

SHRINKAGE PRODUCED BY THE TECHNIQUE WHEN THE POSTERIOR AND ANTERIOR LOBES WERE SEPARATED FROM EACH OTHER.

Autopsy Number.	20–446.		20–450.		22–140.	
Lobe...........	Anterior.	Posterior.	Anterior.	Posterior.	Anterior.	Posterior.
Original volume, c.c...........	.3632	.1415	.3113	.1057	.2547	.1113
Final volume, c.c..	.2430	.0950	.1928	.0666	.1540	.0691
Shrinkage, c.c. ...	.1202	.0465	.1185	.0391	.1007	.0422
Per cent. of shrinkage...........	33.1	32.9	38.1	37.0	39.5	38.0

This is a method which has been used extensively for similar purposes in this and other laboratories and especially by Godlewski, Hammar and Jackson, and the senior author has used it on the hypophysis of the woodchuck. Whether any time would be saved by measuring the areas with a planimeter has not yet been determined on this material. Dr. C. M. Jackson, of this laboratory, after comparing the two methods, favored the cutting-out process. The planimeter cannot increase the accuracy providing one has dexterity with the scissors.

For a differential count of the types of cells in pars anterior, a 5-μ section from each of the three planes mentioned is stained with Mallory's connective tissue stain, going rapidly through the alcohols following the stain. No better differential stain could be wished than this will give on material only a few hours post mortem. These three sections are systematically explored with an oil-immersion lens by means of a mechanical stage, and the cells of each type in each fifth field of each fifth row (as shown in Fig. 1) are counted and the percentage of the total calculated.

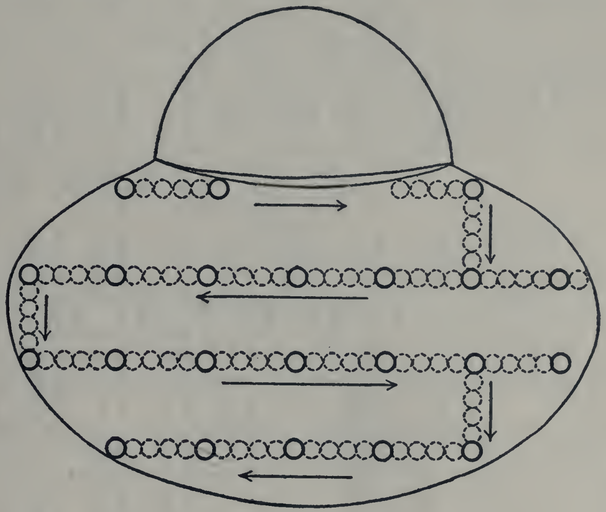


FIG. 1. Diagram showing how the field is explored in making the differential count of cells in pars anterior. The solid circles represent the fields which are actually used.

RESULTS.

In Table II are recorded some selected cases to illustrate what the method yields in four normal males with hypophyses covering the usual range in weight met with, one female with a rather large hypophysis and one case of non-neoplastic post-adolescent hypopituitarism of both lobes. The small normal male hypophysis (Nos. 21–66) is seen to have an especially small pars nervosa (posterior lobe). The great size of the female hypophysis

TABLE II.

WEIGHT AND PERCENTAGE OF THE VARIOUS PARTS OF THE HUMAN HYPOPHYSIS.

Cases.	Autopsy Number..	20–323.		20–380.		21–68.		21–66.		21–14.		22–81.	
	Age........	36 yr.		37 yr.		50 yr.		58 yr.		53 yr.		59 yr.	
	Sex........	Male.		Male.		Male.		Male.		Female.		Male.[1]	
Weight of Whole Gland (grams)................		.530		.660		.585		.420		.830		.620	
		grams.	%	grams.	%	grams.	%	grams.	%	grams.	%	grams.	%
Pars Anterior (Distalis)	Trabeculae .	.0043	.84	.0032	.49	.0099	1.70	.0072	1.71	.0159	1.92	.0022	.34
	Parenchyma	.3832	72.30	.4501	68.20	.3743	63.99	.2859	68.08	.6339	76.37	.4678	75.45
	Total......	.3875	73.14	.4533	68.69	.3843	65.69	.2931	69.79	.6498	78.29	.4700	75.79
Pars Nervosa (Proc. Infund.) or Posterior.......		.1120	21.13	.1538	23.30	.1319	22.54	.0722	17.20	.1248	15.04	.0939	15.15
Pars Intermedia (Juxtaneuralis)	Colloid.....	.0046	.86	.0022	.33	.0055	.94	.0036	.86	.0093	1.12	.0101	1.63
	Parenchyma	.0022	.42	.0110	1.67	.0104	1.77	.0040	.95	?	?	.0074	1.20
	Total......	.0068	1.28	.0132	2.00	.0159	2.71	.0076	1.81	?	?	.0175	2.83
Capsule..................................		.0234	4.42	.0389	5.90	.0259	9.05	.0471	11.21	.0460	5.54	.0386	6.22

---

[1] A typical specimen of so-called non-neoplastic post-adolescent hypopituitarism of both lobes (diagnosis by Dr. Wm. O'Brien). 189 cm. long. Weight 330 lbs. 3 hrs. post mortem.

is due to a large pars anterior. The hypopituitary case has a hypophysis very similar in volumetric relations to the female. The absence of data on the parenchyma of pars intermedia of the female hypophysis is due to the fact that the cells of this portion in this particular case were very few and the tissue not fresh enough when fixed to be well differentiated by the stain. This will have to be expected in a few cases since pars intermedia constitutes such a small irregular part of the entire gland—a fact of some consequence in view of Bab's theory that the polyurea in hypopituitarism is due to hyposecretion of the pars intermedia and because in some of the lower forms this part of the hypophysis is distinctly connected with pigmentation. The greatest error will always be in connection with the juxtaneural portion; but the error can be decreased by placing this part of the gland under higher magnification if that should be deemed necessary.

In Table III is shown a typical cell count as obtained by the method here outlined.

TABLE III.

DIFFERENTIAL COUNT OF THE CELLS IN PARS ANTERIOR OF HYPOPHYSIS FROM A 63-YR.-OLD WOMAN (AUTOPSY NUMBER 21–190—3 HR. POST MORTEM).

Total fields from three different levels 150. Sections 5 μ thick. Formalin fixation. Mallory's C.T. Stain.

Cell Types.	All Types Together.	Chromophobes.	Acidophiles.	Basophiles.
Number of cells counted..	25,658	14,776	8,510	2,372
Percentage..............	100	57.6	33.2	9.2

OBSERVATIONS ON THE DEVELOPMENTAL ANATOMY OF THE TEMPORAL BONE*

LEE ROGERS

The development of the temporal bone in later fetal life and childhood, and the varying relations of its several parts at different ages, with particular reference to their surgical significance are considered. In the main, study has been limited to those phases of the subject concerning which information is obviously incomplete or concerning which there is a decided difference of opinion.

MATERIAL AND METHODS

A considerable amount of material was available, including 294 temporal bones, some dried, and some fresh and in place, also a series of thirty-two skulls in various stages of development. Of the temporal bones, fourteen were of fetal stages, thirty-two of newborn, eighteen of children of different ages (two to fifteen years, inclusive), and 230 of adults. Of the skulls, fourteen were fetal, fourteen were of newborn, and four were of children. There was also available a large number of adult skulls for comparison with those of earlier stages. The subject has been attacked with a variety of methods.

1. A series of casts was prepared in Wood's metal, reproducing the cavities of the ear. Forty such casts were prepared. Fifteen of these were ears of adults, five of children, ten of newborn infants, and ten of fetuses (Figs. 188–190).

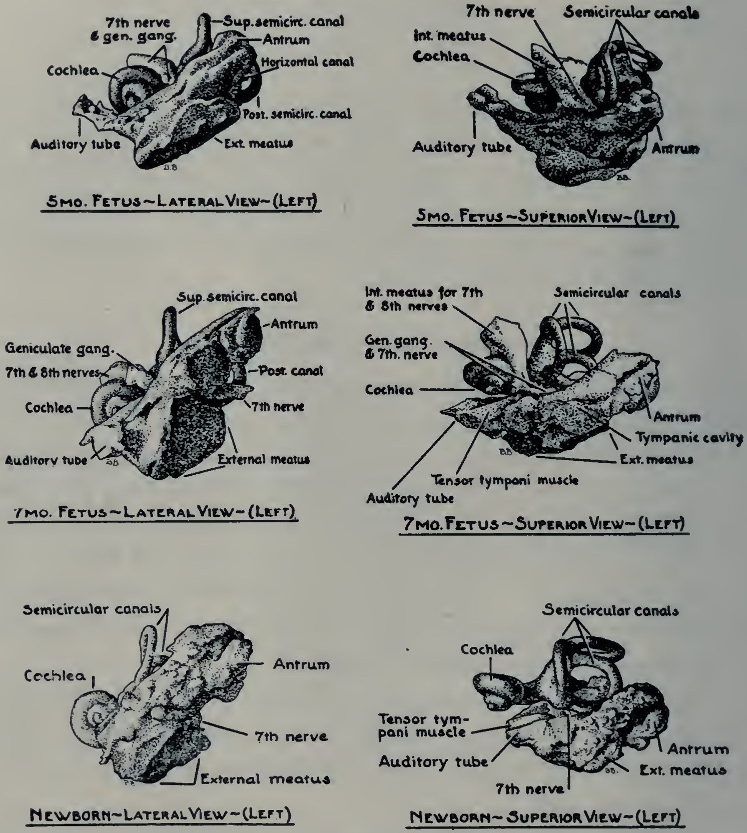
2. The antrums of a series of temporal bones were filled with bismuth paste and roentgenographed to show their position at different ages. As a check on this procedure, the antrums were later transilluminated by introducing the small electric light of a bronchoscope tube in the

---

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1920. Published in full in the Annals of Otology, Rhinology, and Laryngology, 1921, xxx, 103–129. From the Departments of Anatomy and Ophthalmology and Otolaryngology, University of Minnesota, Minneapolis.

cavity of each bone and tracing the outline on the surface. The size and position of the antrums were thus determined by roentgenography and transillumination in forty instances (ten adults, seven children, eight newborn infants, and fifteen fetuses).

3. In order to determine the relations of the inner structures of the ear to surface landmarks, a series of casts was prepared in Wood's metal and the bone in these specimens was later rendered transparent by the Spalteholz clearing method, so that the cochlea, antrums, nerves, air cells, and so forth, could be observed in situ. Three of these preparations were made, one of an adult, one of a child three years old, and one of a newborn infant.



5 MO. FETUS ~ LATERAL VIEW ~ (LEFT)

5 MO. FETUS ~ SUPERIOR VIEW ~ (LEFT)

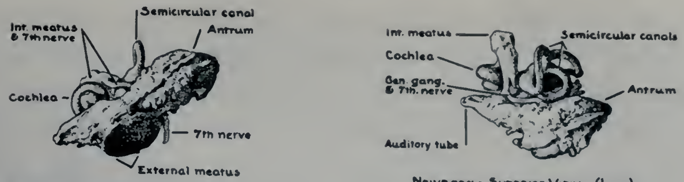
7 MO. FETUS ~ LATERAL VIEW ~ (LEFT)

7 MO. FETUS ~ SUPERIOR VIEW ~ (LEFT)

NEWBORN ~ LATERAL VIEW ~ (LEFT)

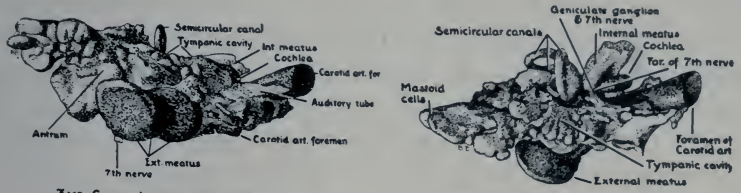
NEWBORN ~ SUPERIOR VIEW ~ (LEFT)

FIG. 188.—Wood's metal casts of internal and middle ear of fetus and newborn; natural size.



NEWBORN ~ LATERAL VIEW ~ (LEFT)

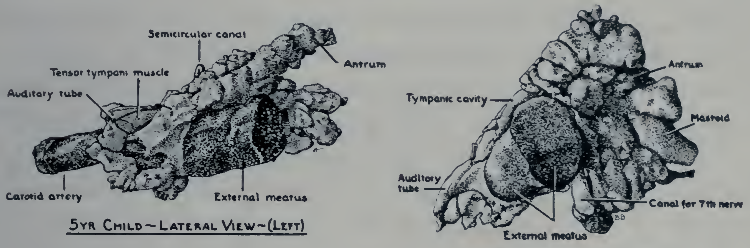
NEWBORN ~ SUPERIOR VIEW ~ (LEFT)



3 YR. CHILD ~ LATERAL VIEW ~ (RIGHT)

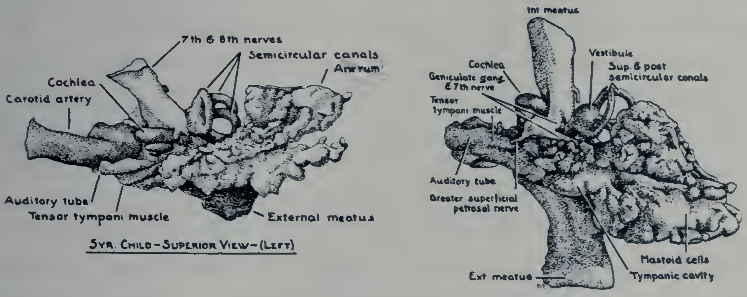
3 YR CHILD ~ SUPERIOR VIEW ~ (RIGHT)

FIG. 189.—Wood's metal casts of internal and middle ear of newborn and child; natural size.



5 YR CHILD ~ LATERAL VIEW ~ (LEFT)

ADULT ~ LATERAL VIEW ~ (LEFT)



5 YR. CHILD ~ SUPERIOR VIEW ~ (LEFT)

ADULT ~ SUPERIOR VIEW ~ (LEFT)

FIG. 190.—Wood's metal casts of internal and middle ear of child and adult; natural size

4. In order further to determine the relations of the antrums, facial nerve, and other structures to the surface landmarks, regional dissec-

tions were made on the cadaver. Of these eight were of adults, two of children, and eight of newborn infants. The angle of inclination of the tympanic membrane was also determined in fifty-five ear drums in six adults, four children, twenty-four newborn, and twenty-four fetuses.

TECHNIC OF MAKING CASTS OF THE TEMPORAL BONE WITH WOOD'S METAL

The value of the study of the middle and inner ear by means of casts has long been recognized, and in making them a variety of materials have been used to replace the air spaces. Benzold used a mixture of wax and resin, Von Stein used a rubber and chloroform solution, and then vulcanized the mass. Brühl cleared the bone and injected mercury. Brown injected dental rubber and vulcanized. Wood's metal seems to give the most satisfactory results for this type of preparation, and certain refinements of the method introduced here have been found of value.

To make casts of the middle and inner ear, it is best to secure well dried temporal bones in which the nerves and mucous membrane of the cavities have disintegrated and disappeared, so that the canals will be clear. If any of these dessicated tissues remain, they should be removed with the air blast. The canals and nerve openings are then covered with adhesive tape, with the exception of the external auditory meatus, which is left open. After heating the encased bone at about 100 C. for twenty-four hours in a sand bath, it is ready to receive the molten Wood's metal, which is poured into it to the level of the suprameatal (Henle's) spine. As the bone is heated above the melting point of the metal, the latter will not solidify, and the specimen can be agitated to remove air bubbles. It is a good plan to drop a little water on the metal at the meatus to solidify it, and then the bone can be picked up, and rotated to remove the air and get the metal into all parts. After cooling, the plaster of Paris casing is removed and the specimen is placed in 30 per cent hydrochloric acid to dissolve the bone.

TECHNIC OF PREPARING TRANSPARENT BONE SPECIMENS

The method used to render the injected specimens of bone transparent is that developed by Spalteholz in 1906. After the temporal bone is filled with Wood's metal, it is decalcified by placing it in a 2 per cent solution of hydrochloric acid, which is changed daily for one month. It is then transferred to a 1 per cent solution of hydrochloric acid which is also changed daily for two weeks. The bone is washed in running water for two weeks, or until it gives a neutral reaction to blue litmus, after which it is bleached for two hours in hydrogen peroxid. After bleaching the specimen is again washed, then dehydrated by passing it through a series of graded alcohol solutions, 60, 75, 95, and 98 per cent. It should be left in each mixture about twenty-four hours. After dehydration, the specimen is cleared by placing it in benzol for four days, and changing the solution at the end of forty-eight hours. The final preserving fluid in which the specimen is to remain consists of methyl salicylate five parts, and isosafrol three parts. As these fluids have the same refractive index as the prepared bone the latter becomes translucent. Sometimes it may be made more transparent by adding a little more isosafrol. Air bubbles may be removed by placing the specimen under a bell jar and exhausting the air with a suction pump.

THE TYMPANIC MEMBRANE

One is confronted with great variance of opinion in the literature with regard to the inclination of the tympanic membrane. Observers seem to be about equally divided as to whether the inclination in the newborn is equal to, or less than that of the adult, and several maintain that the ear drum is almost horizontal at birth. The data obtained by the measurement of individual ear drums is shown in Table 1. The figures indicate the degree of inclination from the perpendicular. The measurements show that a large individual variation is common in both newborn and adult drums. The averages show that the membrane approaches a little more closely the horizontal fetus and that it gradually becomes more erect in later fetal life. There seems to be no constant change in the angle after birth.

The angles given in Tables 2, 3, and 4 were determined with the stangengoniometer of Martin and Ranke. As these measurements were taken to the extreme edge of the sulcus tympanicus they will be found to be slightly larger than the drum membrane proper.

It is a general statement that the dimensions of the tympanic membranes at birth are almost identical with those of the adult, there being little or no increase in the postnatal period of development. The figures quoted in Table 2 show that the tympanic membrane increases steadily in size in the last half of fetal life and that there is a distinct increase in its diameter in the first year after birth, at the end of which period the adult dimensions are attained. (Tables 1 and 2.)

TABLE 1

Dimensions of the Tympanic Membrane and Ring in Prenatal and Postnatal Life

Age.	Cases.	Average maximal diameter, mm.	Average minimal diameter, mm.
Fetal months:			
Four	2	6.8	5.5
Five	3	7.4	6.2
Six	4	7.6	6.7
Seven	3	8.3	7.7
Eight	3	8.9	7.8
Nine	6	9.3	8.2
Newborn	14	9.8	8.2
Seven months	1	11.0	8.5
One year	1	11.0	9.0
Two years	1	11.0	9.0
Adult	6	11.0	9.0

TABLE 2

The Inclination of the Tympanic Membrane in Prenatal and Postnatal Life

Age.	Cases.	Angle of inclination (degrees).		
		Maximum.	Minimum.	Average.
Fetal months:				
Four	2	63	61	62.0
Five	6	80	55	64.4
Six	6	65	58	61.5
Seven	5	63	55	60.2
Eight	5	65	58	61.4
Nine	8	68	55	60.8
Newborn	9	65	54	57.0
Three years	2	60	55	57.5
Adult	6	69	45	57.5

THE ANTRUM

The relations of the antrum to its adjacent structures vary considerably at different ages. Up to the time of birth the antrum is directly over the meatus, its upper part lying above the zygomatic process and its anterior margin extending forward beyond that of the meatus.

In the fetus and newborn the incus lies in the aditus and its long process projects into the antrum. As the child grows older the antrum gradually shifts from its location above the meatus to a more posterior and inferior position, and in the adult it is directly posterior to it (Figs. 191–193). Its position in the child materially aids drainage in acute infections.

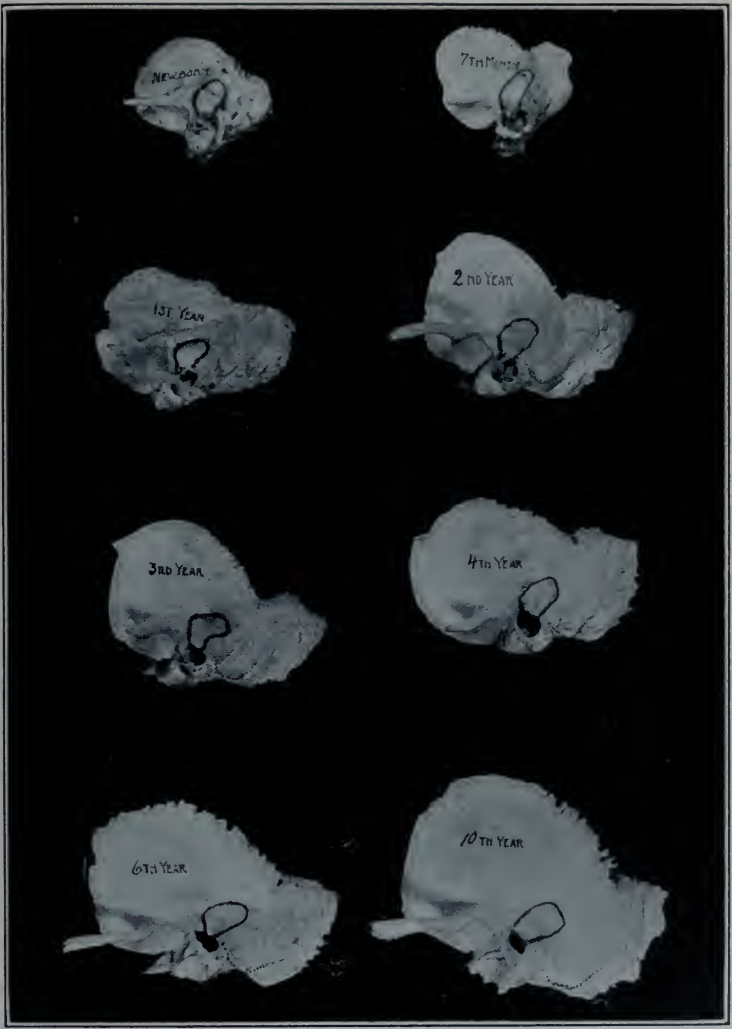


FIG. 191.—A series of temporal bones showing the position of the antrum as determined by X-ray and transillumination.

1. Newborn.
2. Seven months' child.
3. One year old.
4. Two years old.
5. Three years old.
6. Four years old.
7. Five years old.
8. Ten years old.

The lateral (external) canal of the bony labyrinth forms the inner boundary between the antrum and epitympanic recess. Its bony covering is easily recognized as a thin ridge of dense bone. In the

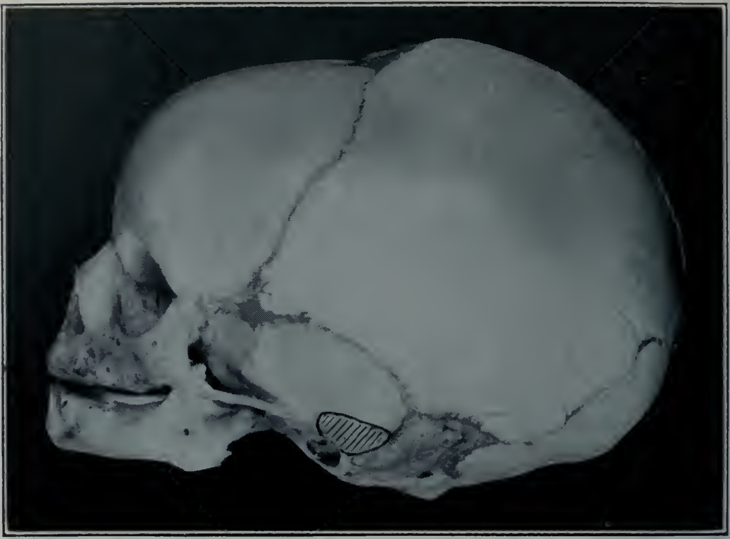


Fig. 192.—Lateral view of skull of newborn child showing position of tympanic antrum as determined by X-ray and transillumination.

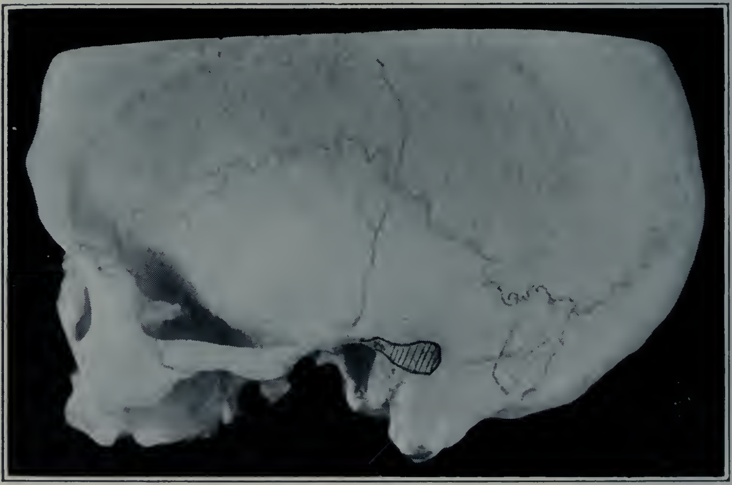


Fig. 193.—Lateral view of adult skull showing position of tympanic antrum as determined by X-ray and transillumination.

young child its wall is only about 0.2 mm. in thickness, and a probe or curette introduced into the middle ear could easily rupture into the canal. The thickness of the bone separating the antrum and lateral canal at different ages is approximately: newborn, 0.2 mm.; child three years old, 0.3 to 0.5 mm.; child five years old, 0.5 mm.; adult, 1 mm.

As the mastoid develops, the antrum becomes farther removed from the external surface of the temporal bone. The thickness of the bony wall bounding the lateral surface of the antrum at different ages is approximately: newborn, 1 to 2 mm.; child five years old, 6 mm.; child ten years old, 10 mm.; adult, 15 mm.

These data are approximately the same as those given by Symington. The dimensions of the antrum in the newborn are about 10 by 11 mm., which is approximately the same as in the adult.

THE FACIAL NERVE

The general course and relations of the facial nerve in the temporal bone are much the same in the infant and adult, and there seems to be a consistent and uniform growth of its parts. The distance from the nerve's entrance into the internal auditory meatus to the central point of the geniculate ganglion is shown in the following: five month fetus, 8 mm.; seven month fetus, 9 mm.; newborn (average of ten cases), 10 mm.; child three years old, 12 mm.; adult (average of ten cases), 13 mm.

The distance from the center of the ganglion to the point where the nerve turns sharply downward is 10 mm. in the newborn, 11 mm. in the child of three years, and an average of 12 mm. in the adult. This portion of the nerve lies within the tympanic cavity, and in its course over the promontory around the fenestra rotundum it is protected only by a thin shell of bone in the adult, and in the child up to the fourth year it is often covered only by a thin membrane of connective tissue. This exposed condition accounts for the liability to facial paralysis in the child following acute otitis media. As the nerve runs directly beneath the anterior part of the external (horizontal) canal, a roughly used probe, or Staeke's director for locating the epitympanic recess may easily injure it. As Cheatle aptly says, "Such an instrument is safe only in experienced hands, and then it is not needed."

The course and relations of the facial nerve can be seen in the superior views of the various casts. The distance from the posterior rim of the tympanic membrane to the nearest point of the facial nerve is from 3 to 5 mm., in the fetus and in the adult.

The exposed condition of the nerve, in early life, after its exit from the stylomastoid foramen, is of importance both to the obstetrician and the surgeon. In the fetus and young infant it emerges about 3 mm.

behind and a little below the most posterior part of the margin of the tympanic membrane. As there is no mastoid process at this time, the nerve runs downward over the petrous portion of the bone. This condition accounts for some of the facial paralyses produced by pressure with instruments at this point during delivery. It is also to be noted that this external portion of the nerve lies in the path of an incision such as is made in operation for mastoiditis in the adult. If such an incision were made in the infant, the nerve would be cut and facial paralysis would result; but as the antrum in the young child is much higher and as there is no mastoid containing air cells, there is little need for such an incision. The relations of the exit of the facial nerve, the antrum, the tympanic membrane, and the developing mastoid process are shown in Figures 191 to 193.

After the first year the vertical portion of the facial nerve is gradually covered by the deposit of the layers of bone forming the mastoid process, and by the outward growth of the posterior portion of the tympanic ring, which forms the osseous meatus. The thickness of the bone over this portion of the nerve is shown by the following measurements: child one year, 0 mm.; child three years, 6 to 10 mm.; child five years, 11 mm.; adult, 13 to 15 mm.

In all fetal and infant specimens examined the nerve came straight to the surface, but, as Freligh says, in some cases the nerve bends downward before emerging, and in these cases the exit would be 2 or 3 mm. lower.

THE INNER EAR

If lines were projected through each posterior canal, they would meet a little posterior to the hypophysis and form approximately a right angle. Likewise, lines through the superior semicircular canals would meet above the posterior rim of the foramen magnum and be approximately at right angles to each other. It can be seen that the canals of one side are at right angles, and that either canal of one side is at right angles to its mate on the other side. This makes the posterior canal of one side parallel to the superior canal of the other and vice versa. On measurement it is found that in only about 33 per cent of the cases are these angles exactly 90 degrees. Other cases will vary 10 degrees above or below.

Lines projected through the superior canal of the newborn meet within the foramen magnum, while in the adult they meet well back of it. This is partly due to the fact that the foramen magnum is more posteriorly located in the infant skull and partly because the superior canal lies more nearly in the transverse plane. The lines running forward through the posterior canals of the newborn meet in the region of the

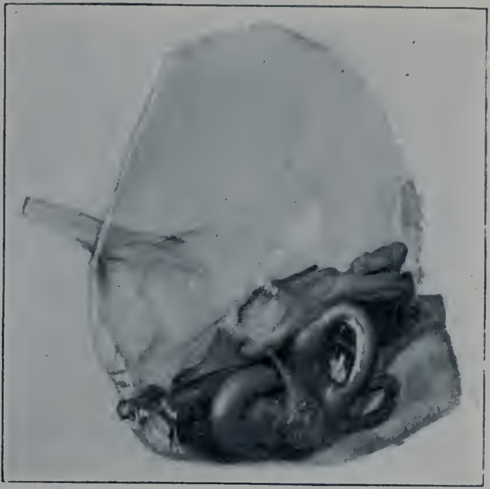


FIG. 194.—Lateral view of temporal bone of newborn child which has been injected with Wood's metal and cleared with Spalteholz's method. (×1½.)

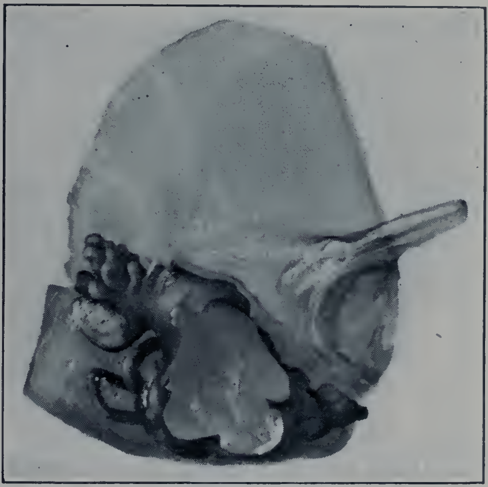


FIG. 195.—Medial view of same specimen as Figure 194. (×1½.)

clivus, while in the adult they meet farther forward in the region of the sella turcica. This is also due to the fact that the posterior canal of the newborn lies more nearly in the transverse plane than that of the adult.

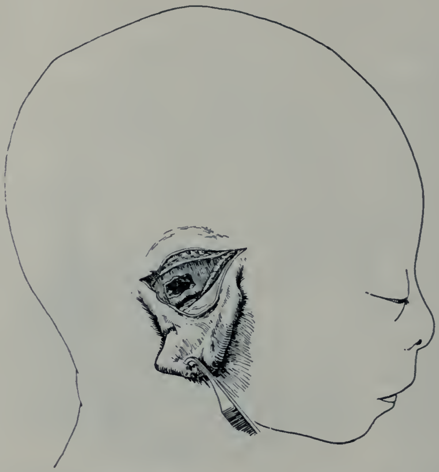


Fig. 196.—Dissection showing position of antrum in relation to external osseous meatus in newborn child.

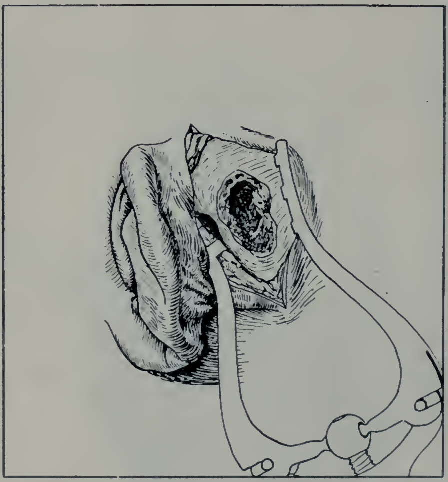


Fig. 197.—Dissection showing position of antrum in relation to the external osseous meatus in the adult.

Alexander and Shaw found the adult inner ear larger than that of the newborn. Boot found the postembryonic growth to be about 18 per cent. Hyrtl found the inner ear of the adult and child about the same size, with an increase in size in old age. The diameters at different ages are shown in Tables 3 and 4. The inner ear changes but little in size after the fifth fetal month.

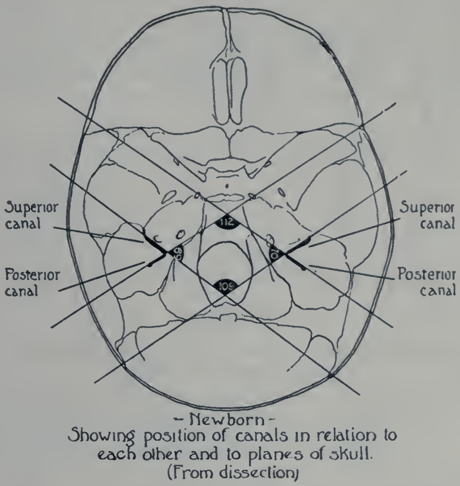


FIG. 198.—Drawing of the base of the skull showing the positions and angles of the superior and posterior semicircular canals in newborn child. (×1½.)

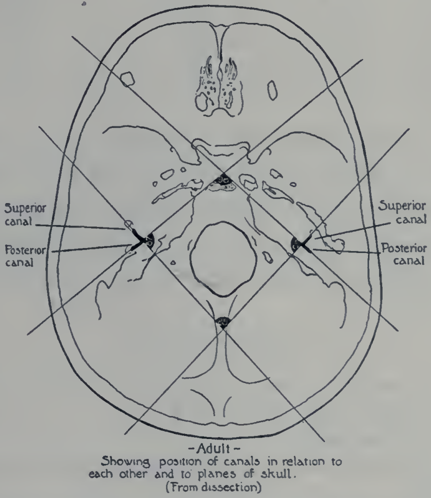


FIG. 199.—Same as Figure 29 of adult skull. (×1½.)

TABLE 3

MAXIMAL LENGTH OF THE INNER EAR, INCLUDING THE COCHLEA, THE VESTIBULE, AND THE POSTERIOR SEMICIRCURAR CANAL

Age.	Author's series, mm.	Length according to:		
		Alexander, mm.	Siebenmann, mm.	Shaw, mm.
Fetal months:				
Five	18			
Seven	18			
Newborn	17	15	19	18
Three years	18			
Five years	16			
Adult	18	18.5	18.5	20

TABLE 4

DIAMETER OF VARIOUS PARTS OF THE INNER EAR AT DIFFERENT TIMES IN PRENATAL AND POSTNATAL LIFE

Age.	Vertical diameter of cochlea, mm.	Horizontal diameter of superior semicircular canal, mm.	Anteroposterior diameter of external canal, mm.	Vertical diameter of posterior canal, mm.
Fetal months:				
Five	7.5	8.0	7.0	8.0
Seven	7.0	7.5	7.0	
Newborn	7.0	8.5	7.0	7.25
Three years	7.5	8.25	7.0	
Five years	7.5	8.5	7.0	8.0
Adult	7.5	8.5	7.0	8.0

The distance of the horizontal canal from the cortex in the infant is from 4 to 6 mm., while in the adult it is from 12 to 20 mm. The horizontal canals and the oval window are the most common points of entrance for infection. The angles of the semicircular canals to each other and their positions in relation to the rest of the skull are shown in Figures 198 and 199.

BIBLIOGRAPHY

1. Alexander, G.: Zur Frage des postembryonalen Wachstums des menschlichen Ohrlabyrinthes. Anat. Hefte, 1902, xix, 571–578.

2. Benzold: Quoted from Brown.

3. Boot, G. W.: Development and structure of the temporal bone. Jour. Am. Med. Assn., 1910, lv, 563–565.

4. Brown, J.: Bull. Med. Department, Washington Univ., 1905, iv, No. 1.

5. Brühl, G.: Eine Injectsmethode des Felsenbeins. Anat. Anz., 1897, xiii, 93–94.

6. Cheatle, A. H.: Some points in the surgical anatomy of the temporal bone from birth to adult life. London, 1897, 131 pp.

7. Freligh, C. A.: A preliminary report on the temporal bone and its anomalies at birth in one hundred and fifty cases. Bull. Lying-In Hosp., 1913, ix, 3–11.

8. Hyrtl: Quoted by Alexander.

9. Shaw, A. J.: A few anatomical and clinical points in the ear of the new-born infant. Ann. Gynec., and Pediat., 1899–1900, xiii, 127–142.

10. Siebenmann, F.: Die Korrosions-Anatomie des knöchernen Labyrinthes des menschlichen Ohres. Wiesbaden, Bergmann, 1890, 61 pp.

11. Spalteholz, W.: Ueber das Durchsichtigmachen von menschlichen und tierischen Präparaten nebst Anhang: Ueber Knochenfärbung. Leipzig, Herzel, 1911, 48 pp.

12. von Stein, S.: [Review of the literature on anatomy and physiology of the ear]. Moskva, 1890.

13. Symington, J.: The mastoid portion of the temporal bone. Edinburgh Med. Jour., 1886–1887, xxxii, 293–298.

MORPHOMETRY OF THE HUMAN FETUS WITH SPECIAL REFERENCE TO THE MEASUREMENTS OF THE HEAD*

LEROY A. CALKINS

A preliminary report of this study was given in Volume one, pages 441–442 of this series. The material there described has been further amplified and strengthened to a total of 369 specimens. The necessary correction for effects of preservation was found by a rather extended series of measurements on fresh specimens, and later on the same specimens during fixation. The effects of birth-moulding were next determined by making a series of measurements on babies born by cesarean section, without the trial of labor, and selected breech extractions. The curves, when finally corrected, resolved themselves into straight lines as previously predicted. The various head measurements, mathematically expressed, are:

Sitting height = 0.66 standing height + 5.0 mm.
Occipitofrontal diameter = 0.235 standing height + 4.0 mm.
Biparietal diameter = 0.19 standing height + 2.0 mm.
Suboccipitobregmatic diameter = 0.2 standing height + 6.0 mm.
Suboccipitofrontal diameter = 0.215 standing height + 7.0 mm.
Occipitomental diameter = 0.235 standing height + 2.0 mm.
Horizontal head circumference = 0.675 standing height + 13.0 mm.
Suboccipitobregmatic circumference = 0.625 standing height + 16.0 mm.
Suboccipitofrontal circumference = 0.65 standing height + 15.0 mm.
Occipitomental circumference = 0.63 standing height + 9.0 mm.
Large circumference = 0.72 standing height + 10.0 mm.

Similar formulæ for other dimensions of the body (as developed simultaneously in this study) enable one to construct an entire fetus at any period of development, if given one of a series of standard dimensions.

---

* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1921. Reprinted from the American Journal Obstetrics and Gynecology, 1922, iv, 109–130. From the Department of Obstetrics and Gynecology and the Department of Anatomy, University of Minnesota, Minneapolis.

Reprinted from the PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE,
1922, xx, pp. 102-104

1022

50 (2010)

The height-weight index of the newborn infant.

By RICHARD E. SCAMMON.

[*From the Department of Anatomy, University of Minnesota, Minneapolis, Minnesota.*]

The material used in this study consisted of the records of the heights (or lengths) and weights of some 4,200 living newborn children from a number of European clinics. The lengths were all in centimeters, the weights in grams. The cases were grouped according to their lengths in centimeter intervals, the group of shortest infants including those from 47 to 48 cm. and the group of longest cases including those from 56 to 57 cm. in length. The males and females of each group were considered separately. The average weight and the standard deviation, the probable error and the coefficient of variability of the weight were determined for each group. The ponderal or height-weight index of the average weight for each group was also worked out according to the formula:

$$\text{P. I. } \frac{\text{Weight}}{\text{Height}^3} \times 1000.$$

These indices were determined both on the pound-inch (avoirdupois) and the centimeter-kilogram (metric) basis. The results obtained are shown in part in the graph below and may be summarized as follows:

(1) With the increase in total body length in the latter part of prenatal life the height-weight index drops slowly, there being a decline of 1.5-2.5 per cent. (avoirdupois index) or 0.4-0.8 per cent. (metric index) between the average for 47 cm. and that

for 50 cm. of total body length. In infants over 50 cm. in total body length the index declines much more rapidly, falling from an index of the average of 89.50 per cent. for males and 88.12 per cent. for females (avoirdupois) at 50 to 51 cm. to one of 79.91 per cent. for males and 80.08 per cent. for females at 56 to 57 cm. of body length. The drop in the metric index for the same period is from 25.99 per cent. to 22.94 per cent. for the males and from 25.60 per cent. to 23.24 per cent. for the females. This agrees with Bardeen's findings[1] that longer newborn infants are relatively lighter than shorter ones, although the values are slightly below those reported by Bardeen. It seems significant that this drop is accentuated after the infant reaches the length of 50 cm. which is generally regarded as a criterion of the completion of the normal span of intrauterine life. Since the ponderal index drops very rapidly with increasing length after 50 cm. the usual empirical formulæ for body length and body height in the fetal period will not hold for these longer infants.

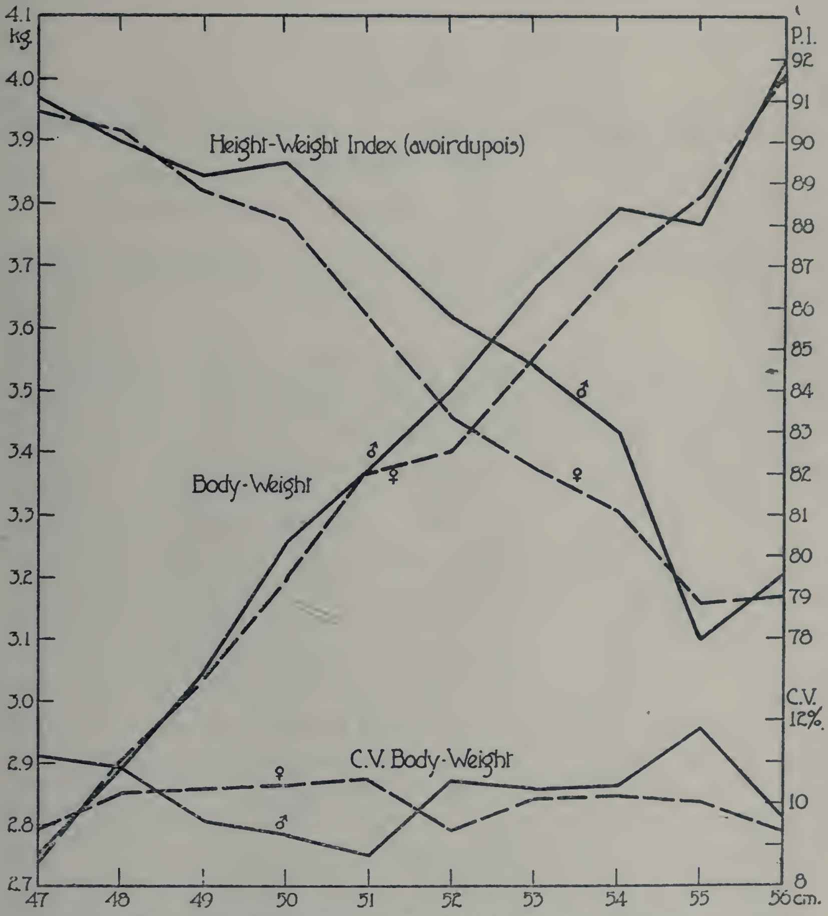
(2) In the majority of the groups of cases the height-weight indices of the males were above those of the females. However, the differences were so small that their significance is questionable.

(3) When the cases are arranged in groups according to centimeter intervals of body length the coefficients of variability in weight of these groups are found to range from 9.5 to 12.0. There is no regular change in the coefficients with increasing body length and no constant sex difference in the coefficient is noted.

The above conclusions were drawn from a study of the ponderal index as determined from the average weight for a given length. The difference between this figure and the average of the *individual indices* for a given length was tested by determining these two values separately for the 50 to 51 cm. group which included 996 cases. In this group the height-weight index of the average height and weight was 25.99 per cent. (metric) for the males and 25.60 per cent. (metric) for the females. The average height-weight index was 26.01 per cent (metric) for the males and 25.60 per cent. (metric) for the females. The average ponderal index of the males showed a standard deviation of 2.41 and a coefficient of variability of 9.27 while that of the females showed a standard deviation of 2.26 and a coefficient of variability of 8.85.

---

[1] Bardeen, C. R., Publ. 272, Carnegie Inst. of Washington, 1919.



A graph illustrating the relation between body length (or height) and body weight in a series of 4,208 living, new-born children. The curves show the average body weight, the coefficient of variability of body weight and the height-weight index for centimeter intervals of body length from 47 to 57 cm. The males are indicated by solid, the females by broken lines.

u

L023
1

Reprinted from the PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE,
1923, xx, pp. 353-356.

172 (2132)

Simple empirical formulae for expressing the lineal growth of the human fetus.

By RICHARD E. SCAMMON and L. A. CALKINS.

[*From the Department of Anatomy, University of Minnesota, Minneapolis, Minnesota.*]

In the quantitative study of the growth of the human body there is often need for simple and accurate formulæ for expressing the relation between body-length and prenatal age. Empirical formulæ for lineal growth in the fetal period (3 lunar months to birth) have been published by Hassee[1], Henry and Bastien[2], and Scammorn[3]. No one of these is entirely satisfactory, for the first gives results which are not in accord with modern findings regarding prenatal lineal growth, the second is highly complicated, and the third is primarily for use in estimating the length from the age, whereas one usually desires to determine the age from the length. Practicable formulæ of this kind should fulfill the following conditions: (a) They should express age in terms of body-length for the entire fetal period (3 months to birth). (b) They should give a close fit to reliable data on the subject. (c) They should be in simple form, which will permit their application with ordinary arithmetic without the use of tables of special functions and the like. With these conditions in mind the following formulæ have been developed on the basis of the data of Mall[4].

---

[1] Hasse, *Charité Ann.*, 1875, ii, 669.

[2] Henry et Bastien, *C. R. Acad. Sc.*, 1904, cxxxix, 811.

[3] Scammon, PROC. SOC. EXP. BIOL. AND MED., 1921, xix, 133.

[4] Mall, Determination of the age of human embryos and fetuses; Keibel and Mall, *Human Embryology*, 1910, i, 199.

When Mall's observations are placed in graphic form they approximate a parabola having the general form: $T = a + bL + cL^2$, where T is the age in fetal or lunar months (calculated from the first day of the last menstruation), L is the total or crown-heel length in cm., and a, b and c are constants. The specific formula for expressing this relations is:

$$(1) \quad T = 2.3 + \frac{2.5\ L}{28} + \frac{L^2}{784}.$$

This may be simplified to:

$$(2) \quad T = (\frac{L}{28} + 1.25)^2 + 0.74.$$

For estimating the crown-heel length from the age, the formula may be transformed into:

$$L = 28\sqrt{T - 0.74} - 35.$$

These formulæ may also be modified for further use. According to Mall, the cohabitation age averages 10 days less than the menstrual age which is estimated from the first day of the last menstruation, and the individual deviations from this average are quite small. Therefore, the formula for menstrual age may be modified to

$$(3) \quad T = 1.94 + \frac{2.5\ L}{28} + \frac{L^2}{784}$$

or

$$(4) \quad (\frac{L}{28} + 1.25)^2 + 0.38$$

to express the cohabitation age.

While the above formulæ are not complicated, somewhat simpler ones may be used for approximate values. These are

$$(5) \quad T = (-\frac{L}{30} + 1.49)^2$$

for estimating age from total length and

$$(6) \quad L = 30\sqrt{T} - 44.7$$

for estimating length from age.

The values given by these various formulæ and their absolute and percentage deviations from Mall's observed values are shown in the accompanying tables.

TABLE I.

Observed and Calculated Body-length of the Human Fetus by Fetal Months.

Age in fetal months	Total body-length by interpolation from Mall's data (a)	Total body-length calculated by exact formula. (b)	Total body-length calculated by approximate formula (c)	Deviation of "b" from "a"		Deviation of "c" from "a"	
				cm.	Per cent.	cm.	Per cent.
3	7.06	7.08	7.26	+0.02	+0.28	+0.20	+2.97
4	15.55	15.54	15.30	—0.01	—0.07	—0.25	—1.67
5	22.53	22.79	22.38	+0.26	+1.15	—0.15	—0.66
6	29.40	29.20	28.79	—0.20	—0.68	—0.61	—2.01
7	35.00	35.05	34.67	+0.05	+0.14	—0.33	—0.94
8	40.83	40.43	40.15	—0.40	—0.98	—0.68	—1.42
9	45.40	45.47	45.20	+0.07	+0.15	—0.20	—0.49
10	50.00	50.20	50.17	+0.20	+0.40	+0.17	+0.34
			Sum	1.21	3.85	2.59	10.50
			Mean	0.15	0.48	0.32	1.31

TABLE II.

Observed and Calculated Age of the Fetus at 5 cm. Intervals of Body-length.

Total (crown-heel) body-length (cm.)	Age in fetal months by interpolation from Mall's data (a)	Age in fetal months as calculated by exact formula (b)	Age in fetal months as calculated by approximate formula (c)	Deviation of "b" from "a"		Deviation of "c" from "a"	
				Fetal months	Per cent.	Fetal months	Per cent.
5	2.71	2.78	2.72	+0.07	+2.58	+0.01	+0.36
10	3.38	3.32	3.29	—0.06	—1.77	—0.09	—2.66
15	3.92	3.93	3.96	+0.01	+0.25	+0.04	+1.02
20	4.605	4.61	4.62	+0.005	+0.10	+0.015	+0.32
25	5.36	5.35	5.38	—0.01	—0.18	+0.02	+0.37
30	6.08	6.03	6.20	—0.05	—0.82	+0.12	+1.97
35	6.95	6.99	7.02	+0.04	+0.57	+0.07	+1.01
40	7.82	7.90	7.95	+0.08	+1.02	+0.13	+1.66
45	8.905	8.90	8.99	—0.005	—0.05	+0.85	+0.95
50	10.00	9.95	9.93	—0.05	—0.50	—0.07	—0.70
			Sum	0.38	7.84	0.65	11.02
			Mean	0.038	0.78	0.065	1.10

Reprinted from the Proceedings of the Society for Experimental Biology and Medicine,
1922, xx, pp. 114-117

1024
1

56 (2016)

Empirical formulæ for the postnatal growth of the human brain and its major divisions.

By RICHARD E. SCAMMON and HALBERT L. DUNN.

[*From the Department of Anatomy, University of Minnesota, Minneapolis, Minnesota.*]

Although several graphs have been published illustrating the post-natal growth of the human brain, as well as a few of the growth of the major divisions of the structure, apparently no attempt has been made to analyze these curves and to develop formulæ for the expression of the relation between brain weight and age between birth and maturity. We have made a series of calculations of this type and have computed empirical formulæ for the growth of the encephalon as a whole, the cerebrum, the cerebellum, and the pons, medulla and mid brain, from birth to 20 years. These formulæ have been determined from the weighted average of male and female brain weights. While it will no doubt be possible to develop slight varients of these formulæ for the weight of the entire brain and of the cerebrum for males and females separately, our data indicate that it is hardly practicable to establish separate curves for the sexes, on the basis of the material now available, for the weight of the cerebellum and the brain stem. Likewise no attempt has been made to correct graphically or mathematically for the effect of disease on the weight of the brain although all records of cases involving any brain pathology were rigidly excluded. The curves and formulæ, therefore, represent the growth of the organ in a hospital rather than in the general population.

When plotted against age and tested graphically all the curves of the postnatal growth of the brain approach hyperbolæ and may be expressed approximately by the general formulæ:

$$Y = \frac{x + c}{a + bx} \text{ or } Y = \frac{x}{a + bx} + c.$$

In these formulæ, Y is the weight of the brain or brain-part, X is the age in years and a, b and c are empirically determined constants.

A total of 2956 observations on the weight of the brain as a whole in the postnatal developmental period were available for study. Of these 317 were of newborn infants and 2639 were of individuals between birth and 20 years. The empirical formula of the curve for these data as drawn by inspection is:

$$0.01 \text{ Encephalon weight (gm.)} = \frac{\text{Age (yrs.)} + 0.315}{0.09 + 0.0692 \text{ age (yrs.)}}$$

The average deviation of the calculated values as determined by this formula from the observed trimester averages for the first year and the observed yearly averages thereafter to 20 years is 18.0 grams, and the average percentage deviation for the same values is 1.75 per cent.

The inspected curve of the postnatal growth in weight of the cerebrum, (1032 cases—108 newborn and 924 from birth to 20 years) is expressed by the formula:

$$0.01 \text{ Cerebrum weight (gm.)} = \frac{\text{Age (yrs.)} + 0.39}{0.12 + 0.00775 \text{ age (yrs.)}}$$

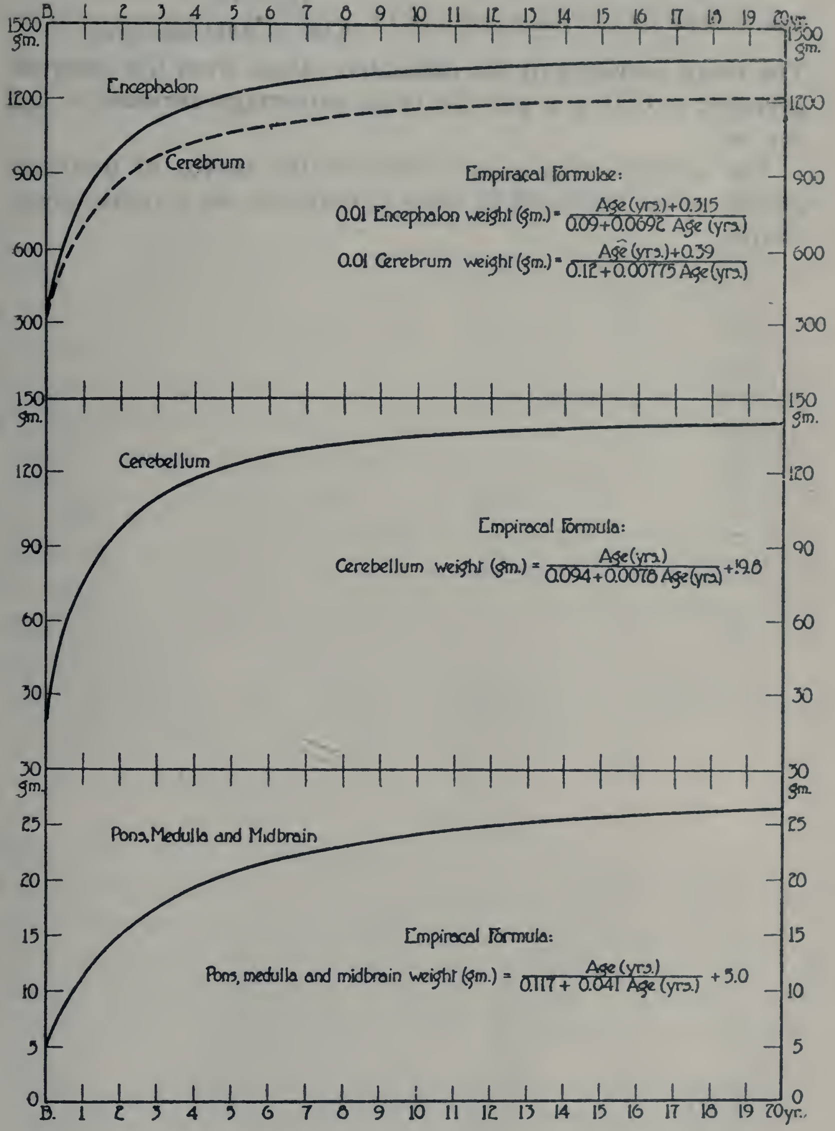
The mean deviation of the calculated from the observed averages for the time intervals as given above is 28.4 grams, and the mean percentage deviation is 2.68 per cent.

The weight of the cerebellum from birth to 20 years (890 cases—99 newborn and 791 between birth and 20 years) may be represented by the formula:

$$\text{Cerebellum weight (gm.)} = \frac{\text{Age (yrs.)}}{0.094 + 0.0078 \text{ age (yrs.)}} + 19.8$$

The mean deviation of the calculated from the observed averages is 3.82 grams and the percentage deviation is 3.72.

The empirical formula for the inspected weight of the pons,


B. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 yr.
1500 gm.
1200
900
600
300
Encephalon
Cerebrum
Empiracal Formulae:
0.01 Encephalon weight (gm.) = $\frac{\text{Age (yrs.)}+0.315}{0.09+0.0692\ \text{Age (yrs.)}}$
0.01 Cerebrum weight (gm.) = $\frac{\text{Age (yrs.)}+0.39}{0.12+0.00775\ \text{Age (yrs.)}}$
150 gm.
120
90
60
30
Cerebellum
Empiracal Formula:
Cerebellum weight (gm.) = $\frac{\text{Age (yrs.)}}{0.094+0.0078\ \text{Age (yrs.)}}+19.8$
30 gm.
25
20
15
10
5
0
Pons, Medulla and Midbrain
Empiracal Formula:
Pons, medulla and midbrain weight (gm.) = $\frac{\text{Age (yrs.)}}{0.117+0.041\ \text{Age (yrs.)}}+5.0$

medulla and midbrain (857 cases—100 newborn and 757 between birth and 20 years) is:

$$\text{Pons, medulla and midbrain weight (gm.)} = \frac{\text{Age (yrs.)}}{0.117 + 0.041 \text{ age (yrs.)}} + 5.0$$

The mean deviation of the calculated values from the observed averages in 0.25 gm. and the mean percentage deviation is 2.2 per cent.

The accompanying graph illustrates the curves of postnatal growth of the brain and its parts as drawn to the formulæ given above.

DEVELOPMENT OF THE MUSCULATURE OF THE STOMACH WITH SPECIAL REFERENCE TO ITS CONDITION IN THE NEWBORN CHILD AND THE PREMATURE INFANT*

ELWYN H. WELCH

The structure and architecture of the muscular coat of the adult stomach of man is well known, as the result of numerous researches in which a variety of procedures and technics have been employed. This knowledge of the structure of the organ has been well correlated, as a whole, with its motor functions through studies by means of roentgenographic and other physiologic technics. However, we have almost no precise information with regard to the development of the muscle architecture of the stomach and its condition at birth and during infancy. Most of the observations on the embryology of the gastric musculature are in scattered notes or statements incidental to studies on other phases of the stomach; while our knowledge of its condition in the newborn seems to be represented by a few statements in older literature on pediatrics. The study was undertaken with the hope of determining the history of the gastric musculature in the embryo and the fetus, and its condition in the newborn and young infant.

MATERIAL AND METHODS

The data which form the basis of this paper have been derived from the study of serial sections of human embryos from glycerin preparations and microscopic dissection of thirteen fetal stomachs, and ten stomachs of the newborn and neonatal period. The sectioned material from the collection in the Anatomical Laboratory of the University of Minnesota, includes a well distributed series of embryos from 5 to 158

---

* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1922. From the Department of Anatomy, under the direction of Dr. Richard E. Scammon, University of Minnesota, Minneapolis.

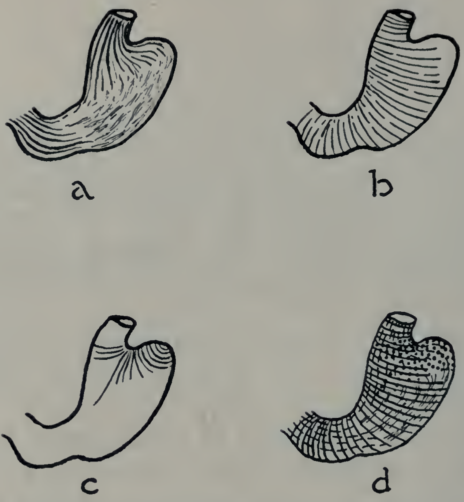


FIG. 1.—Anterior surface of the cleared and dissected stomach of an embryo 61 mm. in crown-rump length. (× $1\frac{1}{3}$.) a. Longitudinal layer. b. Circular layer. c. Oblique and circular fibers of the fundus. d. Longitudinal and circular layers, and oblique and circular fibers of the fundus.

(Note: The above explanation of the different muscular layers of the stomach, designated a, b, c, and d, applies to all figures from 1 to 14.)

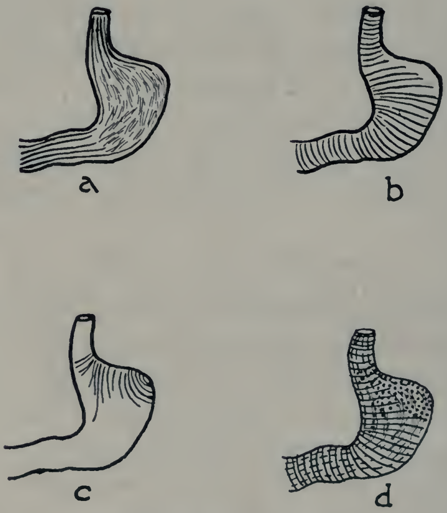


FIG. 2.—64 mm. (× $1\frac{1}{3}$.)

FIGS. 2 to 10 are cleared and dissected stomachs from embryos of the following crown-rump lengths.

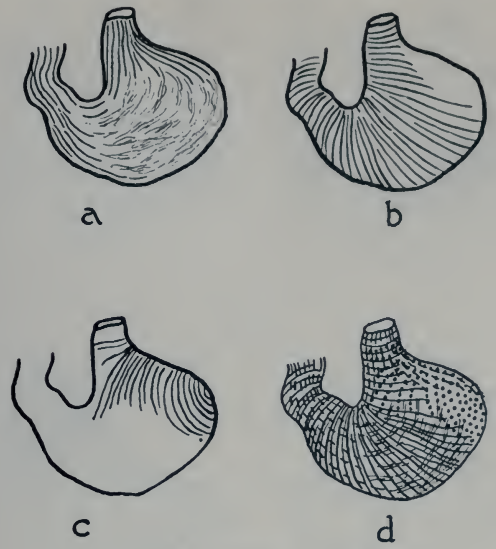


Fig. 3.—65 mm. (× 1⅓.)

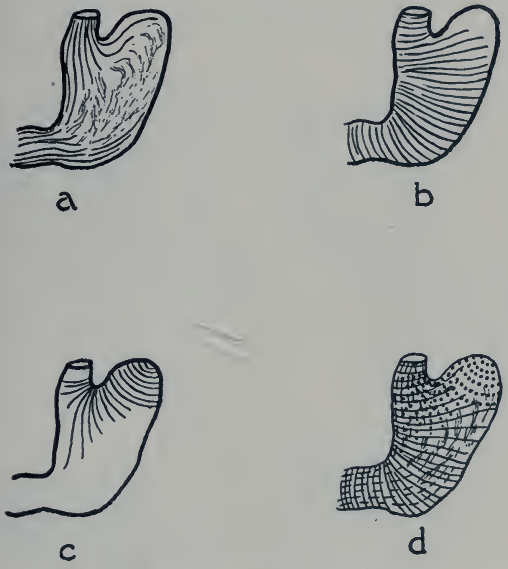


Fig. 4.—95 mm. (× 1⅓.)

mm., crown-rump length. Fetal stomachs, studied grossly, were from fetuses of 61 to 175 mm., crown-rump length. A series of dissections were also made of stomachs of infants from three to ten months of age.

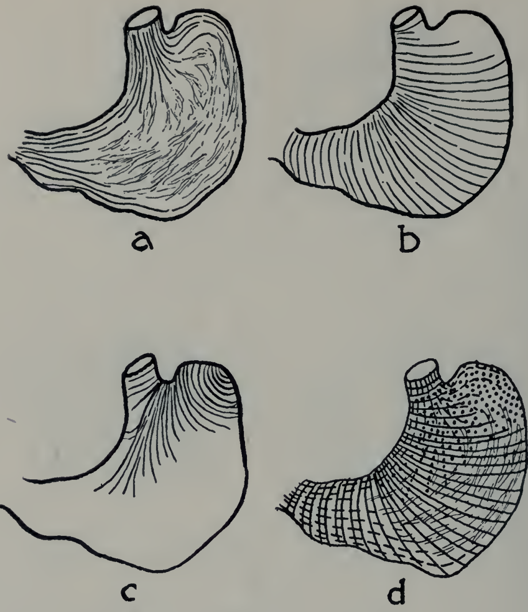


Fig. 5.—107 mm. (× 1⅓.)

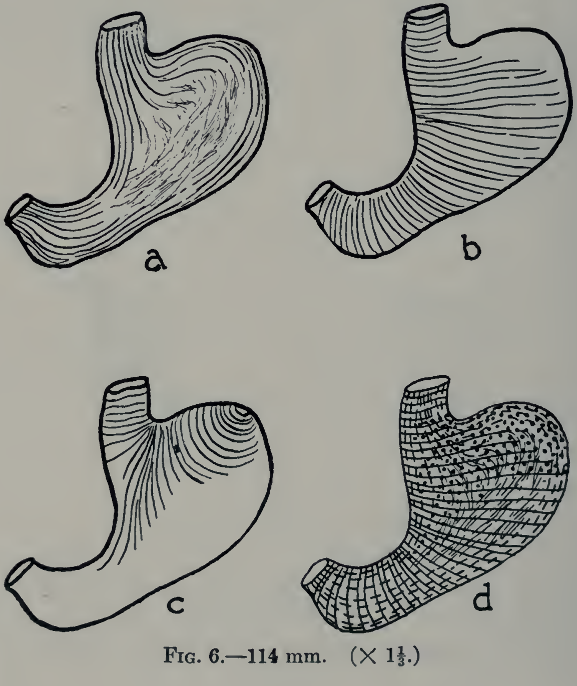


Fig. 6.—114 mm. (× 1⅓.)

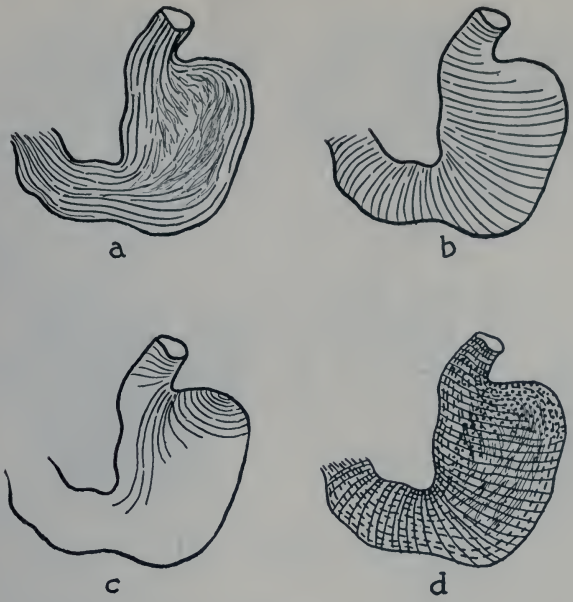


FIG. 7.—129 mm. (× 1.)

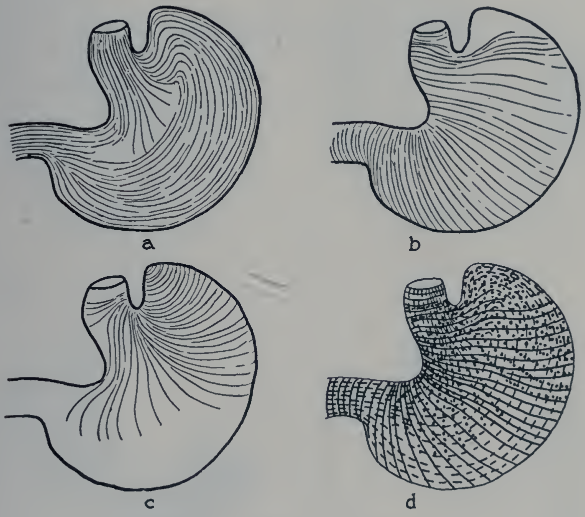


FIG. 8.—148 mm. (× 1.)

The glycerin preparations were first opened, the mucosa carefully removed by scraping and the specimens placed in borax carmin for twelve hours. They were immersed in a half glycerin, half water mix-

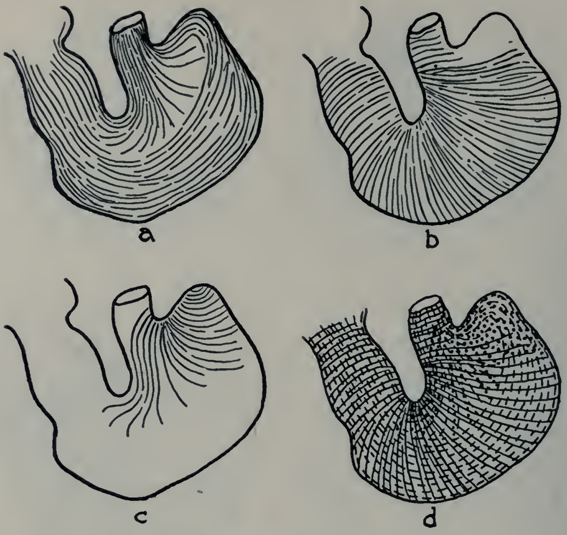


FIG. 9.—165 mm. (× 1.)

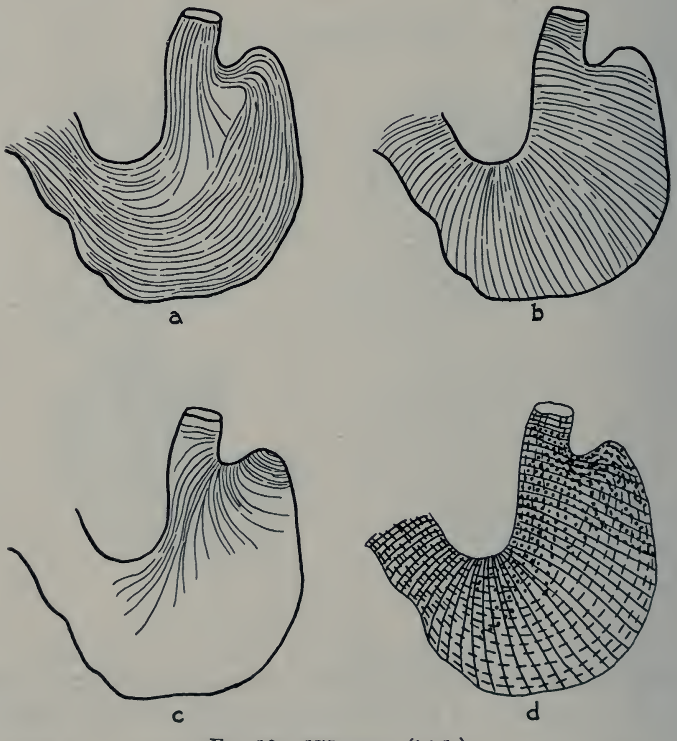


FIG. 10.—175 mm. (× 1.)

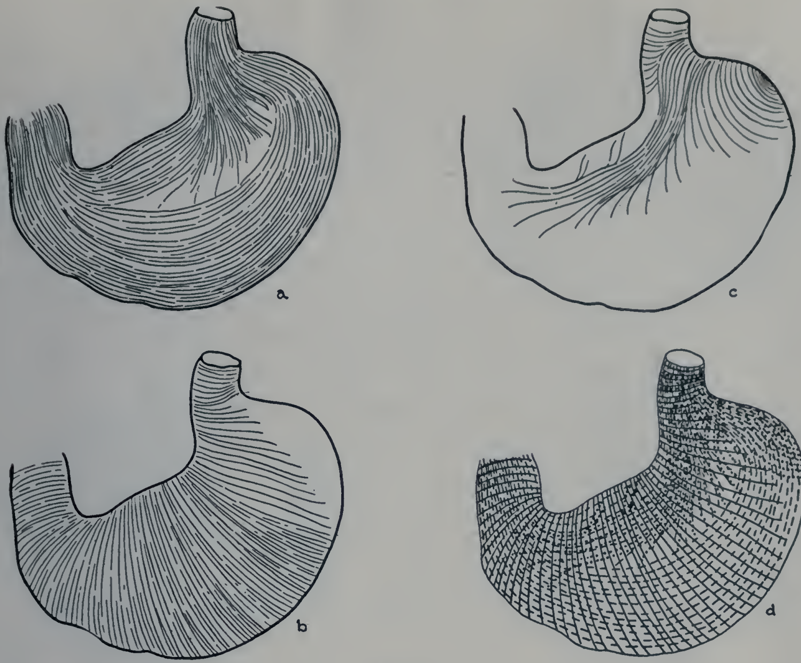


Fig. 11.

Figs. 11 to 14.—Stomachs of newborn; dissected after clearing in glycerin. (× 4/5.)

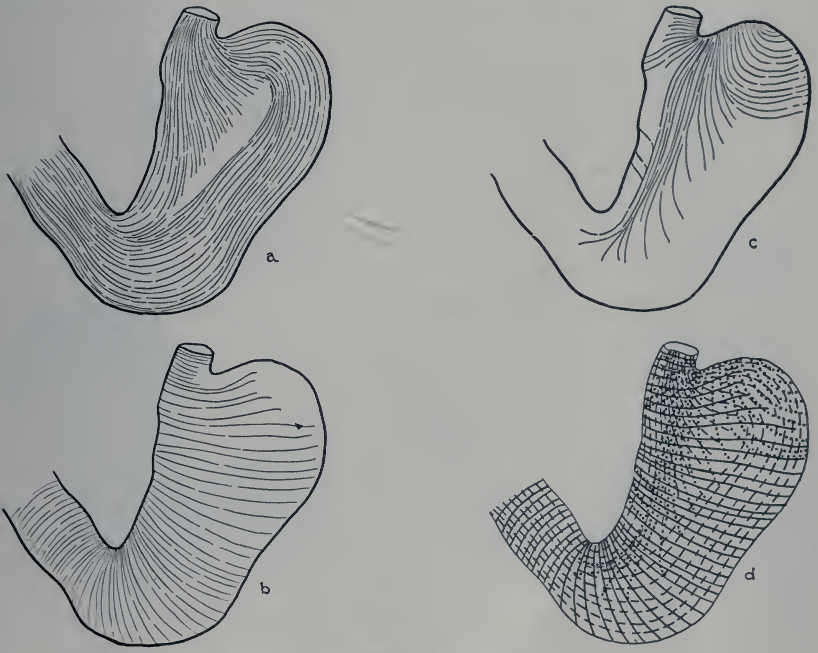


Fig. 12.

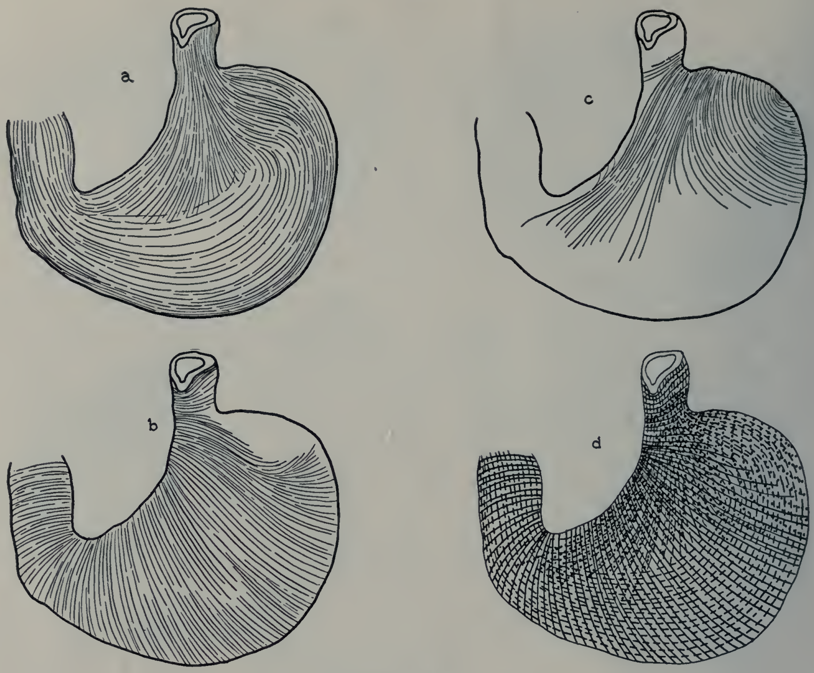


Fig. 13.

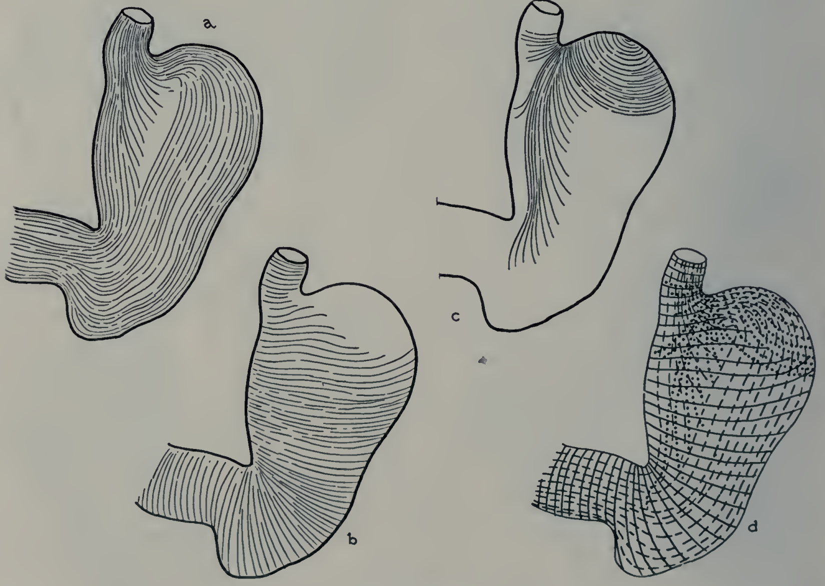


Fig. 14.

ture until thoroughly saturated, carried through dilutions of two parts glycerin and one part water, and three parts glycerin and one part water, to pure glycerin. When spread on a glass plate on the binocular or microscope stage and illuminated from below by a fairly strong light, material prepared in this manner showed the individual muscle bundles very clearly.

In order to facilitate microscopic dissection, all of the stomachs thus studied were placed in a solution of 5 per cent nitric acid in 70 per cent alcohol to loosen the connective tissue. Afterward they were moderately distended with either gelatin or plaster of Paris. The muscle layers were then explored with extremely fine points and forceps, traced in their course and relations, and finally removed, a bundle at a time. This method is somewhat laborious and tedious, but it has advantages over other methods for certain phases of the work. Of the two distension mediums, plaster of Paris is decidedly the more satisfactory, mainly because of its permanency. Any injury to the mucosa through the circular muscle layer readily permits effusion of the gelatin and consequently deflation of the organ, making this filler highly inconvenient.

LITERATURE ON THE DEVELOPMENT OF THE MUSCULATURE OF THE STOMACH

Very little is known of the early formation of the muscular layers of the stomach. Lewis described the development of the outer layers of the stomach beginning with a 10 mm. embryo. At this stage the three layers composing the gastric wall are entodermal epithelium, mesenchyma, and peritoneal epithelium. The circular portion is the earliest of the muscle layers to appear and is first differentiated by a condensed zone of the mesenchyma in embryos of 16 mm. While it can be identified over the greater portion of the stomach, it is best defined along the lesser curvature. According to Broman, Tandler has described this stage at 13 mm. Completion of the circular layer with the appearance of a tunica propria characterizes embryos of 22.8 mm. This stage also shows a slight thickening toward the pylorus, while a prolonged gradual thickening, followed by an abrupt thinning at the duodenum is demonstrable at 37 mm. and in all subsequent stages.

The first "inner longitudinal" bundles appear in the region of the cardia and fundus in 91 mm. embryos.[8] The first mention of such fibers by Giannelli and Lampronti is in a fetus of five months. At this stage at the level of the pylorus one can see running in the circular layer "les petits faisceaux des cellules musculaires lisses obliques" of which some reach almost to the submucosa. "Ces petits faisceaux *ne sont pas en continuité* avec les fibres de la couche musculaire longitudinale."

At 120 mm. Lewis has followed the longitudinal layer of the esophagus for a short distance over the cardia external to the circular layer. However, at this stage the greater portion of the stomach has only the circular layer. In the region of the pylorus there is a distinct outer longitudinal layer at 240 mm. which is much thickened toward the duodenum. Some of its fibers are described as being continuous with the more superficial layer of the duodenum, while the deeper fasciculi appear to turn into the thick circular layer near the pylorus to form the "dilator pylori" described by Cunningham.

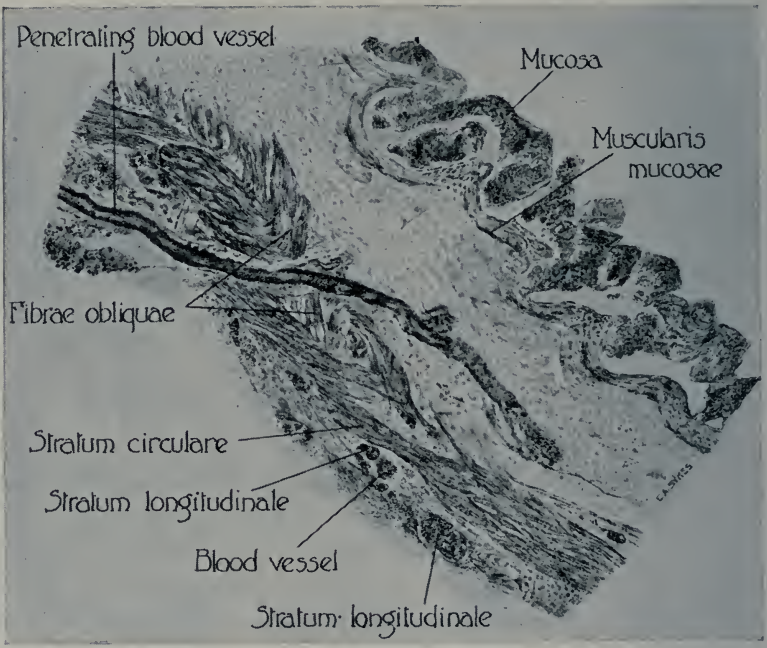


FIG. 15.—Section through mid-ventral wall of the stomach in the region of the cardia. From an embryo of 65 mm. crown-rump length. (× 130.)

Taguchi studied two embryos, one 144 mm. and the other 234.3 mm. in length. The muscular tunic of the former consisted of a circular layer and a longitudinal layer. The latter showed the presence of oblique fibers as well as the longitudinal and circular layers.

One of the few papers describing the stomach of the newborn was published by Fleischmann, in 1875, as follows:

"The ring musculature of the esophagus surrounds the cardia in eccentric circles which become gradually weaker; they circle to the right, bringing the center to the left periphery of the cardia.

"The principal direction of the descending longitudinal fibers of the esophagus, which are superficial to the circular fibers, is towards the small curvature, in the middle of which they diverge toward the aforementioned longitudinal fibers, running laterally, and here disappear underneath them.

"The intrinsic musculature of the stomach consists of compact but freely anastomosing fibers arranged about the main axis in ring formation. These show at the two extremities of the stomach an irregular relationship towards each other.

"The child's stomach does not have oblique fibers; I also note, after some growth, the absence of longitudinal fibers which Henle has found in adults. These are said to originate from the pyloric valve."

THE EARLY HISTORY OF THE GASTRIC MUSCULATURE

The development of the circular layer. The development of the stomach from its first appearance as an expansion of the primitive gut, already described at 6 mm., up to the establishment of the circular layer at 24 mm., is characterized by a rapid growth of the organ with a continuous diminution in the relative thickness of the mesenchmya of its walls. At 6 mm. the thick lining epithelium of columnar cells shows four rows of nuclei, and the surrounding mesenchymal cells, while somewhat scattered and unorganized, are slightly condensed and mark the first appearance of the stratification of the gastric wall. The histologic picture at 7 and 7.5 mm. is essentially the same as in the 6 mm. embryo. At 11 mm. differentiation has already begun and the myoblasts can be seen arranged circularly, while the mucosa has become relatively thinner. The dorsoventral and lateral diameters of the stomach rapidly become greater and at 12 mm. the myoblastic layer is markedly thickened in the region of the future circular layer. From 12 to 17 mm. there is a remarkable growth of the stomach. In the former stage the gastric wall still consists of three primitive layers, entodermal epithelium, mesenchyma including a myoblastic layer, and peritoneal epithelium. The latter stage, however, shows a further condensation of the mesenchyma indicating an actual transformation to circular fibers which is best defined along the right side of the cardia and on the lesser curvature, but which can be identified over the greater portion of the organ. Between this condensed zone and the lining epithelium is a uniform layer of the mesenchyma invaded by numerous blood vessels and nerves.

The circular layer is complete at 24 mm. and is definitely thickened over the pylorus. The fundus has already developed and is completely invested with a layer of the circular fibers. The fibers of the fundus are arranged around a short seam at its apex, around which they describe circles with gradually increasing diameters (Fig. 1, c). Inferiorly, along the greater curvature, they blend imperceptibly with those of the circular layer which surrounds the rest of the organ. Superiorly, over the cardiac incisura, as the diameters of the fiber circles increase they cannot be distinguished from the oblique fibers which lie in this angle;

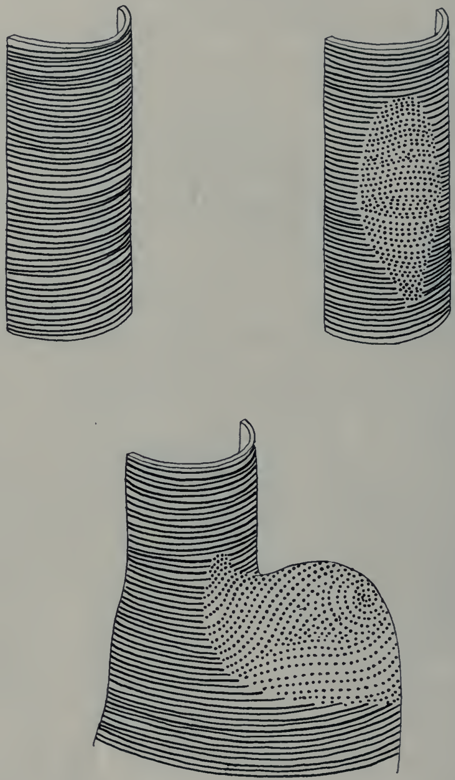


Fig. 16.—Scheme illustrating the formation of the oblique fibers and the circular layer of the fundus.

while on the anterior and posterior walls as these circular fibers approach the corpus they become intermediate between the oblique fibers and the "true" circular layer. This arrangement was checked by graphic reconstruction (Fig. 17), and concurs with dissections of fetal stomachs. At this stage (24 mm.) another condensation of the mesenchyma marks the beginning of a lamina propria. Increased vascularization is everywhere apparent.

At 33 mm. the gastric wall shows a general increase in the circular fibers. The cells are more elongated and the sarcoplasm nearly obscures the nuclei. With continuous growth and differentiation the 41 mm. embryo shows a very high degree of organization in which the circular layer begins to exhibit continuity among its fibers. Together with an increased blood supply to the submucosa there appear scattered patches of a lamina muscularis mucosæ.

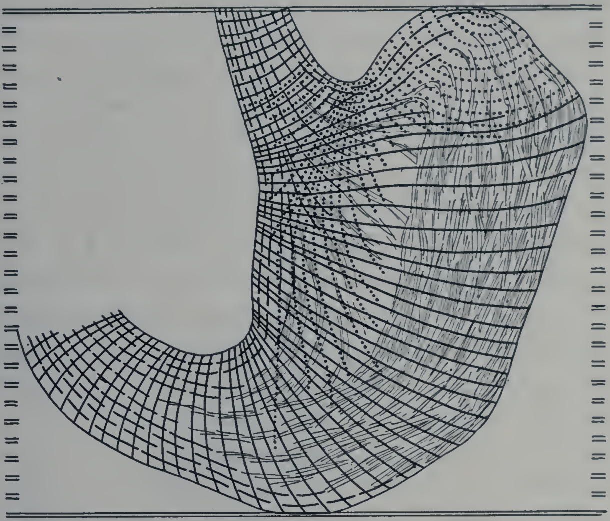


Fig. 17.—Diagrammatic representation of a graphic reconstruction. Stomach of an embryo of 65 mm. crown-rump length. (× 8.) (The double horizontal lines represent every fifth section.)

The last stage at which I studied the circular layer microscopically was in an embryo of 65 mm. Here I found a wide band of well formed circular fibers constituting a well defined, continuous coat pierced by numerous blood vessels which extend well around the greater curvature. The gastric wall measured 0.04 mm. in thickness, approximately one-fourth of which was occupied by the circular layer. The wall of the sphincter pylori measured 0.08 mm. and here the circular layer was 0.03 mm. in thickness. The lamina muscularis mucosæ was still incomplete, but could be identified in all sections.

THE LONGITUDINAL LAYER

The outer muscle coat appears first in more or less discrete, scattered bundles instead of as a simultaneous differentiation over the entire stomach, as is the case with the circular layer. Its subsequent development is much less precocious than that of the circular layer. At 17 mm. groups of cells can be seen just outside of the circular layer over the lower portion of the esophagus and certain parts of the stomach, especially along the margin of the lesser curvature and a short distance over the walls. Cells occupying the same position in the 24 mm. embryo show relatively small nuclei (in transection) surrounded by a dark area of differentiated cytoplasm. This is still more evident at 33 mm. and there is no doubt as to the presence of darkly staining myofibrillæ. The relations of these areas of differentiated mesenchyma to the vascular distribution are a constant feature. The entire gastric wall becomes progressively more vascular and blood vessels are very numerous in the region just outside the circular layer. Grouped about these vessels are areas of differentiated mesenchymal cells. Some of these are developing interstitial connective tissue cells, while the remainder constitute the foundation of the longitudinal section. In 100 sections taken at random in an older embryo (65 mm.), ninety-three demonstrated this feature without exception. The remaining seven showed the relationship to vessels, but at the same time showed certain scanty areas which apparently were independent of the vascular supply. In the 41 mm. embryo there is an increase both in number and distribution of the groups of muscle cells except over the mid-ventral and mid-dorsal portion of the walls of the corpus. In this situation they are very sparsely scattered and in some sections entirely absent. The increase is particularly apparent at the pylorus where there is an intermingling of the cells of the longitudinal layer and the circular layer. At 65 mm. a fenestrated layer of muscle, connective tissue, and blood vessels constitutes the longitudinal layer. Over the lesser curvature this layer is almost uninterrupted except for occasional penetrating vessels and nerves. Wide intervals occupied by connective-tissue cells only are found scattered over the rest of the organ. The continuity of the muscle-cell groups forming a syncytial layer is demonstrated by the graphic reconstruction shown in Figure 17. Within these groups are persistent aggregations of interstitial connective-tissue cells which appear to be very intimately related to the muscle elements of the layer.

THE OBLIQUE FIBERS

The oblique fibers appear as early as 24 mm. as a band of fibers coursing across the cardiac incisura and continuing in the direction of the digestive tube. With the very first appearance of a fundus there is obviously the beginning of a cardiac incisura. Even in these early stages when the circular layer is just differentiating from the mesenchyma of the digestive tube, a solid band of fibers can be seen covering the cardiac incisura. This band extends on the anterior and posterior walls, continues in the direction of the long axis of the stomach, and gradually disappears in the proximal part of the pylorus.

As the rings of the circular layer of the esophagus descend there is an interruption in their continuity in passing from the esophageal to the gastric wall. This interruption may be seen on the left side of the esophagus where the digestive tube expands to form the fundus. These fibers represent the beginning of the oblique fibers. The uppermost fibers are directly continuous with those of the esophagus. As this band approaches the fundus, its fibers are on the same plane with the circular layer and pass imperceptibly into it (Fig. 1, c). The oblique fibers merely represent a specialized part of the primitive circular layer and when the stomach is but a simple tube they cannot be identified as a separate entity. Once differentiated (24 mm.), however, the oblique fibers develop rapidly, and at 33 mm. may be seen in sections almost to the pylorus. At 41 mm. they are increased both in number and length. In the 65 mm. embryo they form a well developed band which is approximately 1.1 mm. in width in the middle of its course, while the lateral diameter of the stomach is only 4 mm. The oblique fibers terminate by joining the circular layer in the direction of the greater curvature (Fig. 15). With the exception of a few strands which course across the lesser curvature this band has the appearance of a unipenniform muscle (Fig. 5, c).

THE GASTRIC MUSCULATURE OF THE FETUS AND THE NEWBORN

The following observations on the later development of the gastric musculature were made chiefly on gross specimens. Of these, two were from embryos of 61 and 64 mm. (Figs. 1 and 2), and the remainder were from fetuses and newborn as previously listed. The results of this study, besides revealing the subsequent development of the muscle layers, afford an excellent check on the material studied in serial sections.

THE CIRCULAR LAYER (FIGS. 1 TO 14)

The arrangement of the circular fibers after their establishment at 24 and 33 mm. remains practically unchanged in all the later stages. The circular layer is well developed at birth and constitutes the greatest part of the gastric musculature. Its fibers are arranged in parallel rings approximately at right angles to the long axis of the organ. If traced downward from the esophagus there is a division of the circular layer into superficial and deep fibers about 5 mm. above the esophageal orifice. The latter will be discussed in connection with the oblique fibers. The former, crossing the subjacent oblique fibers at right angles, continue a short distance toward the fundus and are soon lost among the peripheral fibers of the "fundic whorl." The circular layer is disposed in concentric circles over the corpus and the pylorus, with closely set and freely anastomosing bundles of fibers. Numerous vessels and nerves pierce the gastric wall, especially along the curvatures, producing characteristic openings in the circular layer (boutonnières or Gefässlöcher). During the first year, probably as the result of increased activity of the stomach, there is marked thickening of the circular layer.

THE LONGITUDINAL LAYER (FIGS. 1 TO 14)

The development of the longitudinal muscular coat is not complete until the first year of postnatal life. During the fetal period and in the infant it is present as a coarsely fenestrated layer covering the entire stomach, excepting possibly a small area on the mid-dorsal and mid-ventral surfaces. This "bare area," however, becomes progressively smaller and in some instances among infants nearly two years old it may be entirely covered. For descriptive purposes the longitudinal layer is divided into three parts: first, those fibers which are continuous with the longitudinal layer on the left of the esophagus and pass over the fundus and the greater curvature to the pylorus; second, the fibers which occupy a similar position on the right side of the esophagus and course over the lesser curvature; and third, the intermediate group which cover the anterior and posterior walls to a varying degree.

The first group is directly continuous with the longitudinal layer of the esophagus and extends uninterruptedly in a uniform layer over the cardiac incisura on the dome of the fundus. Long strands of fibers can be stripped as far as the fundic apex where they are afforded an attachment. Likewise fibers of the greater curvature can be stripped to the apex, but very few, if any, actually cross it. This is explained by the presence of a narrow seam or raphé across the top of the fundus at right angles to the longitudinal fibers. (This raphé is often loosely referred to as the point of origin of the circular layer.) Here the ends of longitudinal fibers are bound down by a large amount of connective tissue. Fibers passing on either side of this area do not exhibit such an interruption, but continue to the pylorus in sweeping curves parallel to the greater curvature.

The second group of longitudinal muscle fibers is decidedly the best developed and can be stripped free from the underlying circular layer, without difficulty, from the esophagus to the pylorus. As the stomach narrows to form the pyloric antrum the first two groups are brought together forming a complete cylinder of longitudinal fibers covering this part of the organ.

The third group of longitudinal muscle fibers follows a course intermediate between the first two. As its fibers spread out in a fan-shaped manner they are often ill defined and many merge with the circular layer beneath (Fig. 12, d). In other specimens (Fig. 12, a), where these fibers are better developed, they pass behind the first group and blend with the subjacent circular fibers. When this is the case the entire gastric wall is invested with the longitudinal layer. After birth there is a notable increase in all three groups belonging to the longitudinal layer.

THE OBLIQUE FIBERS (FIGS. 1 TO 14)

After the longitudinal and circular layers of the corpus and pylorus are removed, there remain the oblique fibers and the circular fibers of the fundus. It will be remembered that at the time the circular layer is differentiated the anlagen of both the oblique and the circular fibers of the fundus are represented. At this time, 17 mm., there is only a slight suggestion of a fundus; however, the digestive tube is completely surrounded by an early circular layer. As the fundic diverticulum pushes to the left and upward the fibers which formerly covered it in parallel strands become festooned over this new formed dome (Fig. 16). Coincident with this development there appears a cardiac incisura and a bending of the lower circular fibers of the esophagus. This change in direction corresponds with the angle formed by the circular fibers of the right and left sides of the cardia, shown in all dissections. The latter band of fibers can soon be traced well along the gastric canal in the direction of the pylorus. If considered from the standpoint of simple mechanics the interrelationship and continuity of the layers of muscles of the stomach are much more easily understood.

The oblique fibers become separated from the circular layer at 24 mm. After surrounding the left side of the cardia, they pass beneath the circular layer. At first these fibers are very rudimentary, scarcely covering the narrow cardia. This stage is followed by a period of rapid development, and at 85 mm. (Fig. 3) the oblique fibers can be dissected free almost as far as the incisura angularis. From 85 mm. until birth there is a gradual increase in the number and extent of the oblique fibers, and their permanent relationship is established. In the newborn the oblique fibers extend as far as the pylorus and in some instances actually reach the proximal portion of the sphincter of the pylorus. The inferior fibers of this group (those lying adjacent to the circular layer of the fundus) are short and terminate early by passing into the circular layer and its surrounding connective tissue in the direction of the greater curvature. The remaining oblique fibers which course toward the pylorus are longer and have similar insertions at variable distances. On the side of the lesser curvature in the newborn certain of the oblique fibers invariably joined the circular layer (Fig. 11, c). Similarly, annular fibers belonging to the oblique layer encircle the lower end of the esophagus beneath the circular layer. The only change in this layer during the first year is the accumulation of a greater number of fibers, especially along the gastric canal. There is commonly an alteration in the form of the stomach after birth; it becomes elongated and slightly dilated. As a result the oblique fibers also become longer and the width of this band is increased.

SUMMARY AND DISCUSSION

The findings presented in this paper differ in certain fundamental respects from those in the literature. The first appearance of the transformation from the mesenchyma to muscle fibers may be made out at 17 mm., or at about seven weeks. At 33 mm., or about nine weeks, the longitudinal fibers are definitely established, and there is a relatively wide band of oblique fibers crossing the cardiac incisura. In the ebryos of 41 and 65 mm. (nine and one-half and twelve weeks old respectively) there is an intimate intermingling of the longitudinal and circular fibers at the pylorus, suggesting the formation of the "tug muscle" (dilator pylori) as described by Cunningham. Thus, from nine to twelve weeks on, throughout subsequent development, the musculature of the stomach consists of three parts: the longitudinal and circular layers and the oblique fibers.

The limitation of the stomach musculature to two layers, as by Hyrtl (Gyllenskoeld), holds true for only a very short time. At about 17 mm., when the gastric musculature begins to form and before the appearance of the fundus, I could observe but two layers, the longitudinal and the circular. However, in subsequent stages, after the stomach had assumed its characteristic form (at nine weeks), the third layer of oblique fibers is universally present. At no time can four layers (Guéneau de Mussy) be demonstrated. Any such classification can only be for physiologic purposes. The simple arrangement of the longitudinal layer as given by Sappey has been shown to be inaccurate. Contrary to Larger, the fibers of this layer can be followed in a more or less continuous band over the fundus. While a few can be seen terminating at the apex, others appear to take origin at this point and continue over the greater curvature. The description of the musculature of the adult stomach as given by Birmingham and Forssell, more nearly coincides with the condition found in the fetus and newborn.

The arrangement of the gastric musculature of older human fetuses and the newborn may be summarized as follows: The stomach is everywhere covered (as by the oblique fibers on the mid-dorsal and midventral surfaces) by two layers of muscle, in some places by three. This is true of the dorsal and ventral surfaces of the walls of the cardia and along either side of the lesser curvature. The circular layer is well developed and forms an almost complete layer around the gastric tube. The term "almost complete" is used advisedly because the circular fibers covering the cardiac incisura and on the lower extremity of the esophagus are considered as a separate layer, the oblique fibers. The longitudinal layer usually covers the entire stomach, but is very thin, particularly along the greater curvature and on the dorsal and ventral surfaces. In the latter positions it may even be absent. Beneath the longitudinal and circular layers are the oblique fibers. On the left side of the esophageal-cardiac juncture, the region of the cardiac incisura, the oblique or innermost layer bears the same relation to the digestive tube as the circular fibers on the right side. This band is continuous above with the deep circular fibers of the esophagus and below with the circular fibers of the fundus. Its fibers course over the lateral wall in the direction of the pylorus and finally become a part of the overlying circular layer. The layer of oblique fibers is not of uniform width or thickness, but adapts itself to changes in position and function.

At birth there is a marked dilatation of the stomach due to constant swallowing of a large amount of air, and after the infant begins to nurse there is a further increase in gastric capacity together with a slight change in the form of the organ. A general thinning of the musculature, particularly of the walls and the fundus, results. The relationship of the layers of muscle, however, remains unchanged at three months. During the latter half of the first year (ten months) there is slight compensation through the rapid postnatal growth of the organ, but the gastric wall is still extremely thin and more easily dilated (artificially) than the fetal stomach.

The methods of growth and development differ somewhat in the various layers of the musculature of the stomach. The circular layer is differentiated from the mesenchyma in situ as a sheet surrounding the entire gastric epithelial tube. The longitudinal layer develops as maculations of myoblasts over the stomach and these later anastomose. This confluence gives rise to the fenestrated arrangement characteristic of the stomach in the fetus and newborn. Usually these collections of myoblasts arise in close relation to the larger vascular sprigs in this region. The oblique fibers, as such, begin in a limited area on the left side of the cardia and extend along the gastric canal after the formation of the fundic diverticulum.

CONCLUSIONS

1. The fundament of a muscular coat of the stomach is first observed at 17 mm. (about seven weeks).

2. At the time muscle fibers first appear in the gastric wall, there are but two fundamental layers: the longitudinal and circular.

3. The circular layer of the fundus appears to form concentric whorls about a central raphé as the result of the rapid growth of that part. The actual appearance of annular fibers was not observed until during the first part of the fetal period.

4. Coincident with the development of the fundus (24 and 33 mm.,

eight and nine weeks), the number of layers is increased to three by the development of oblique fibers from the circular layer.

5. The development of the longitudinal fibers is intimately related to the vascular supply to the gastric wall.

6. In the later fetal months the musculature of the stomach consists of: (a) a circular layer completely investing the organ; (b) a coarsely fenestrated longitudinal layer, very thin or absent over the mid-dorsal and mid-ventral portions of the wall; and (c) oblique fibers marking a primitive gastric canal as far as the incisura angularis.

7. The stomach of the newborn is characterized by a very thick circular layer. The longitudinal layer is less scattered than in the fetus, and usually covers the entire organ. The oblique fibers can be traced to the proximal portion of the sphincter of the pylorus.

8. Changes in the stomach musculature during the first year include an interstitial increase in all three muscle layers. The slight alteration in the form of the stomach has no effect upon the relationship of the three layers.

BIBLIOGRAPHY

1. Birmingham, A.: The arrangement of the muscular fibers of the stomach. Jour. Anat. and Physiol., 1898–1899, xxxiii, 22–30.

2. Broman, I.: Normale und abnorme Entwicklung des Menschen. Wiesbaden, Bergmann, 1911, 828 pp.

3. Cunningham, D. J.: The varying form of the stomach in man and the anthropoid ape. Tr. Roy. Soc. Edinburgh, 1906, xlv, 9–47.

4. Fleischmann, L.: Klinik der Pädiatrik. Wien, Braumüller, 1875, i, 171 pp.

5. Forssell, G.: Ueber die Beziehung der Röntgenbilder des menschlichen Magens zu seinem anatomischen Bau. Hamburg, Lucas, Grafe and Sillem, 1913, 277 pp.

6. Giannelli, L., and Lampronti, G.: Le development du pylore humaine. Arch. ital. de biol., 1915, xliv, 284–285.

7. Guéneau de Mussy, N.: Recherches sur la structure de la tunique musculeuse de l'estomac. Gaz. med. de Par., 1842, x, 2 s., 353.

8. Gyllenskoeld, O.: Über die Fibræ obliquæ in dem Magen. Arch. f. Anat. u. Physiol., 1862, 132–139.

9. Larger, R.: Essai critique et expérimental sur les muscles lisses en général et sur quelques-uns en particulier; leur anatomie, leur physiologie normale et pathologique. Strasbourg, Heitz, 1870, 109 pp.

10. Lewis, F. T.: The form of the stomach in human embryos. With notes upon the nomenclature of the stomach. Am. Jour. Anat., 1912, xiii, 477–503.

11. Sappey, P. C.: Traité d'anatomie descriptive. 2 ed. Paris, 1874, iv.

12. Taguchi, H.: Folia anatomica Japonica, 1922, i, 23–39.

A STUDY OF THE PATHOLOGIC CONDITIONS ENCOUNTERED DURING AND FOLLOWING THE RELIEF OF EXPERIMENTAL OBSTRUCTIVE JAUNDICE COMPARED WITH SIMILAR PATHOLOGIC CONDITIONS IN MAN*

LEO P. BELL.

My experiments were conducted for the purpose of studying the effect on the liver of obstruction of the common bile duct and the regenerative processes which occurred after the flow of bile was reëstablished.

In summarizing data from the literature from studies of cirrhosis in man, and of portal and biliary cirrhosis produced experimentally in rabbits and dogs, the following points are emphasized:

1. Many chemical irritants and mechanical means, including twenty-four different technics, have been used to produce experimental cirrhosis.

2. The response of the liver depends on the nature of the irritant or poison and the manner of application.

3. To produce cirrhosis parenchymal cells must be destroyed by mechanical means, such as ligation of the common duct, or by the introduction of toxic substances through the portal vein.

4. Experimental cirrhosis in animals is comparable to that found in man, with regard to parenchymal cell destruction, biliary duct proliferation, connective tissue proliferation, and parenchymal cell regeneration. The microscopic and macroscopic pictures are otherwise dissimilar.

5. Cirrhosis in man is due to a combination of factors which have not been identified experimentally.

6. Cirrhosis in man is due to attempts to repair damage done by successive waves of toxins producing parenchymal cell destruction through the blood stream and biliary apparatus. It is assumed that this chronic process or cell injury covers a considerable period of time.

---

* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1921. From the Section on Experimental Surgery, Mayo Clinic.

University of Minnesota.
Dept. of Anatomy.
Contributions.

244695
Minnesota, University of. Dept. of Anatomy
Contributions.
Vol.8(1922/23)
P
Med
M
Biological
& Medical
Serials

University of Toronto
Library

Biological
& Medical
Serials

DO NOT
REMOVE
THE
CARD
FROM
THIS
POCKET